each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n equals zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$; and

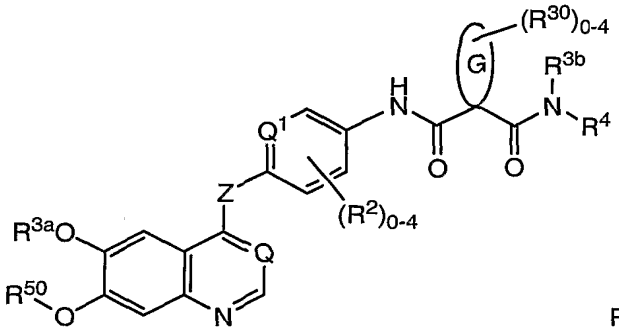
each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl.

[0087] In one example, the compound is according to paragraph [0086], wherein Z is either -O- or $-NR^5-$.

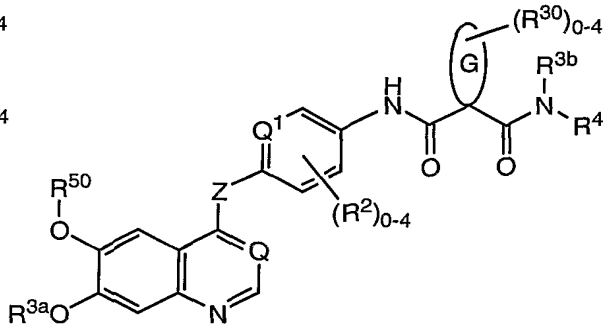
[0088] In another example, the compound is according to paragraph [0087], wherein at least one of R^1 is $-D-R^{50}$.

[0089] In another example, the compound is according to paragraph [0088], wherein D is -O- and at least one other R^1 is $-OR^3$.

[0090] In another example, the compound is according to paragraph [0089], of formula **XIIIa** or **XIIIb**:



XIIIa



XIIIb

wherein Q^1 is either =N- or =C(H)-.

[0091] In another example, the compound is according to paragraph [0090], wherein R^{50} is selected from C_{1-6}alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted C_{1-6}alkyl amino, optionally substituted C_{1-6}dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

[0092] In another example, the compound is according to paragraph [0091], wherein R^{3a} is C_{1-6}alkyl.

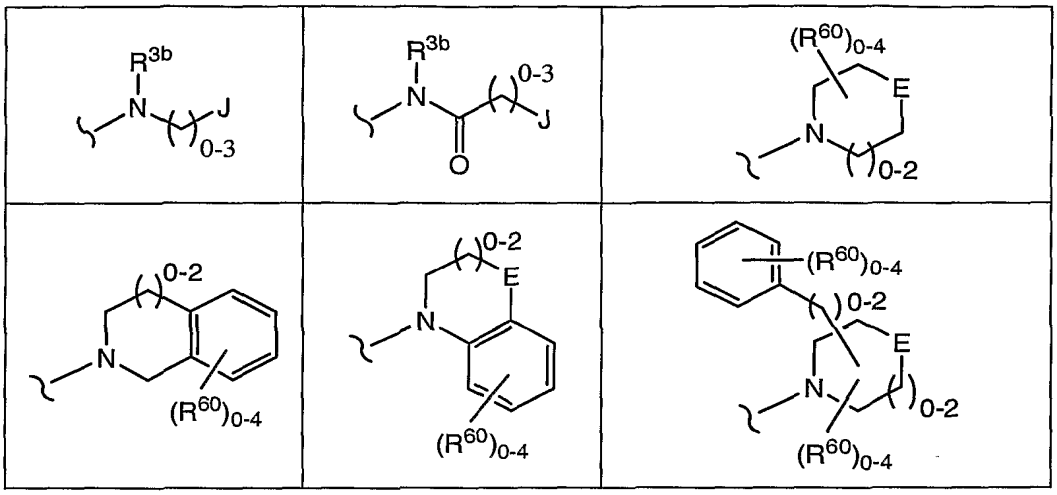
[0093] In another example, the compound is according to paragraph [0092], wherein Z is -O-.

[0094] In another example, the compound is according to paragraph [0093], wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of R^{30}.

[0095] In another example, the compound is according to paragraph [0094], wherein Q is either =N- or =C(H)-.

[0096] In another example, the compound is according to paragraph [0095], wherein R^2 is selected from -H, halogen, C_{1-6} alkyl and perfluoro C_{1-6} alkyl.

[0097] In another example, the compound is according to paragraph [0096], wherein $-N(R^{3b})R^4$ is selected from the following:



wherein J, is a five- to ten-membered ring, optionally substituted with between zero and five of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl;

two of R^{20}, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to J or fused to J;

E is selected from -O-, $-N(R^5)$-, $-CH_2$-, and $-S(O)_{0-2}$-;

each R^{60} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and

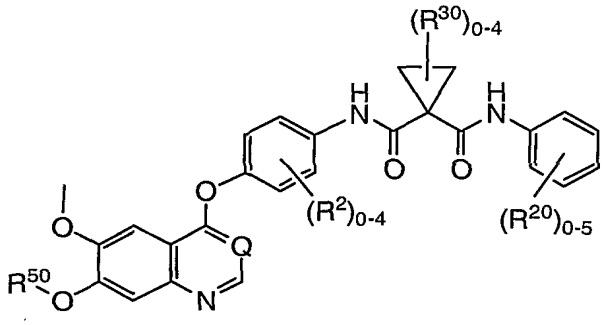
R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; or

two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic;

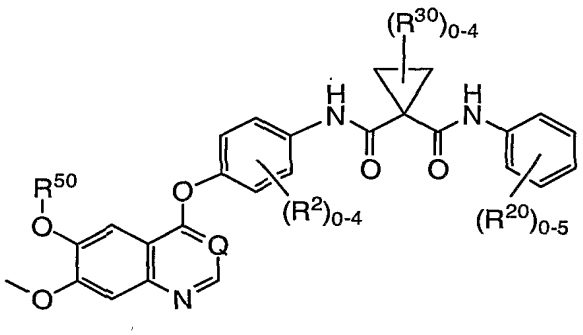
R^{3b} is equivalent to R^3 as defined above; and

R^4 and R^5 are as defined above.

[0098] In another example, the compound is according to paragraph [0097], of formula **XIVa** or **XIVb**:



XIVa



XIVb

[0099] In another example, the compound is according to paragraph [0098], wherein R^{50} is C_{1-6}alkyl optionally substituted with a group selected from optionally substituted amino, an optionally substituted alkylamino, optionally substituted dialkylamino, and optionally substituted heteroalicylic.

[0100] In another example, the compound is according to paragraph [0099], wherein the heteroalicyclic portion of said optionally substituted heteroalicyclic of R^{50} is selected from the group consisting of piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, 2-oxo-morpholine, pyrrolidine, and azepine.

[0101] In another example, the compound is according to paragraph [0099], wherein R^{50} is according to formula **XII**.

[0102] In another example, the compound is according to paragraph [0101], wherein the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

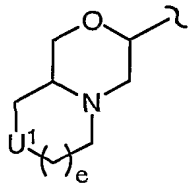
[0103] In another example, the compound is according to paragraph [0102], wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

[0104] In another example, the compound is according to paragraph [0103], wherein n is 0 and the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

[0105] In another example, the compound is according to paragraph [0104], wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

[0106] In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system contains $-NR^8-$, wherein R^8 is selected from -H, optionally substituted C_{1-6}alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0107] In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system is of formula **XV**,



XV

wherein U^1 is selected from $-O-$, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

[0108] In another example, the compound is according to paragraph [0107], wherein Y is $-CH_2-$.

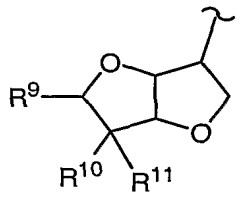
[0109] In another example, the compound is according to paragraph [0108], wherein U^1 is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0110] In another example, the compound is according to paragraph [0108], wherein U^1 is $-O-$.

[0111] In another example, the compound is according to paragraph [0108], wherein U^1 is absent.

[0112] In another example, the compound is according to paragraph [0103], wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

[0113] In another example, the compound is according to paragraph [0112], wherein said saturated bridged ring system is of formula **XVI**,



XVI

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

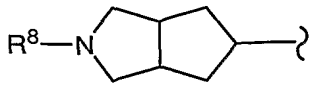
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

[0114] In another example, the compound is according to paragraph [0113], wherein one of R^{10} and R^{11} is $-OR^{12}$, wherein R^{12} is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

[0115] In another example, the compound is according to paragraph [0114], wherein Y is either $-CH_2-$ or absent.

[0116] In another example, the compound is according to paragraph [0113], wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

[0117] In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is of formula **XVII**.



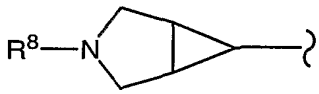
XVII

[0118] In another example, the compound is according to paragraph [0117], wherein Y is either $-CH_2-$ or absent.

[0119] In another example, the compound is according to paragraph [0118], wherein R^8 is methyl or ethyl.

[0120] In another example, the compound is according to paragraph [0119], wherein at least one of R^2 is halogen.

[0121] In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is of formula **XVIII**.

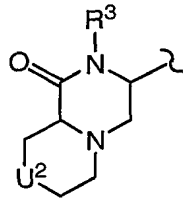


XVIII

[0122] In another example, the compound is according to paragraph [0121], wherein Y is $-CH_2-$.

[0123] In another example, the compound is according to paragraph [0122], wherein R^8 is methyl or ethyl.

[0124] In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system is of formula **XIX**



XIX

wherein U^2 is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

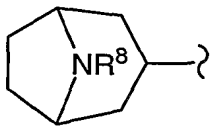
[0125] In another example, the compound is according to paragraph [0124], wherein R^3 of formula **XIX** is selected from -H and optionally substituted alkyl.

[0126] In another example, the compound is according to paragraph [0125], wherein U^2 is either $-CR^6R^7-$ or absent.

[0127] In another example, the compound is according to paragraph [0126], wherein U^2 is either $-CH_2-$ or absent.

[0128] In another example, the compound is according to paragraph [0127], wherein Y is $-CH_2-$.

[0129] In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is according to formula **XX**.



XX

[0130] In another example, the compound is according to paragraph [0129], wherein R^8 is methyl or ethyl.

[0131] In another example, the compound is according to any of paragraphs [0099] – [0130], wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[0132] In another example, the compound is according to paragraph [0131], wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

[0133] In another example, the compound is according to any of paragraphs [0099] – [0130], wherein R^{20} is selected from halogen, $-CN$, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted three- to six-membered heteroalicyclic, said optionally substituted three- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

[0134] In another example, the compound is according to paragraph [0133], wherein R^{20} is selected from halogen, $-NR^3R^4$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted five- to six-membered heteroalicyclic, said optionally substituted five- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

[0135] In another example, the compound is according to paragraph [0134], wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[0136] In another example, the compound is according to paragraph [0135], wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

[0137] In another example, the compound is according to paragraph [0086], selected from Table 2.

Table 2

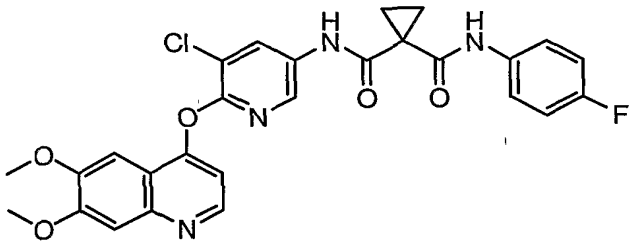
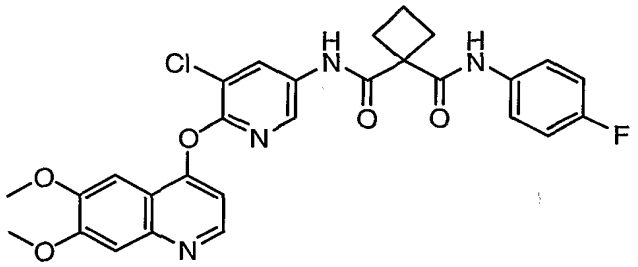
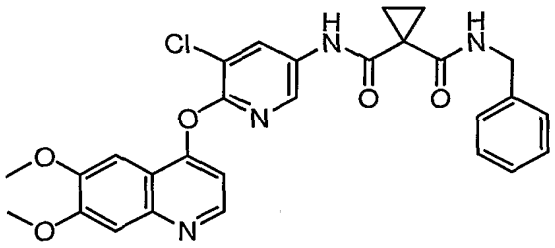
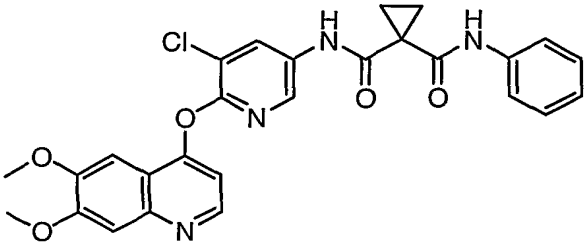
Entry	Name	Structure
1	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
2	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
3	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	
4	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	

Table 2

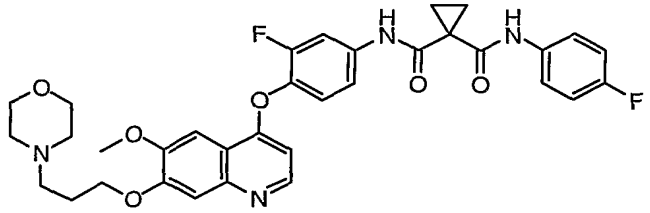
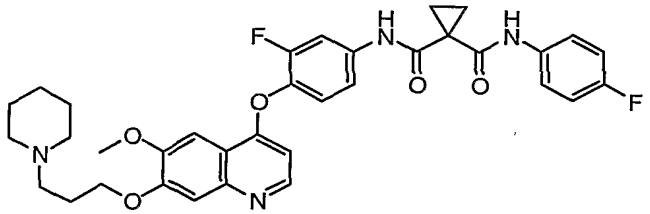
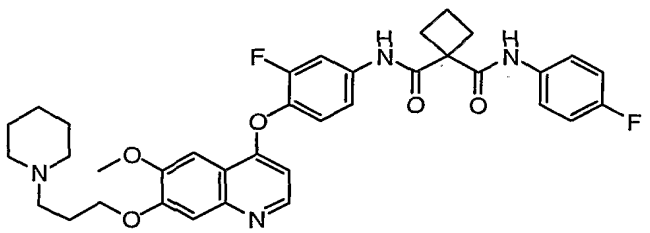
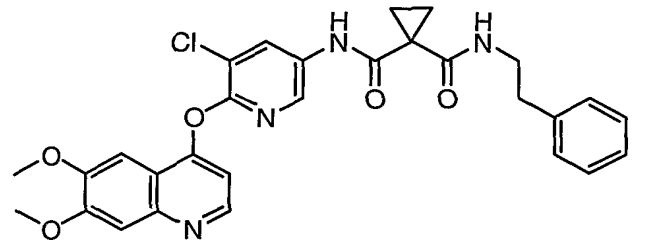
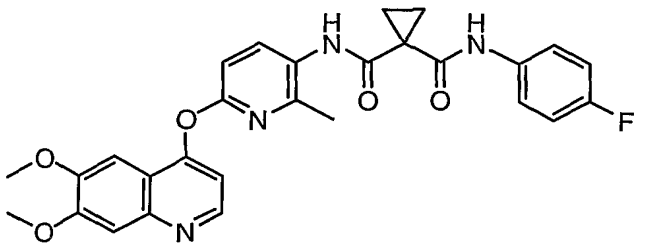
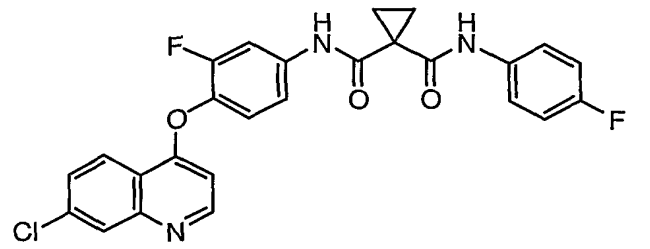
Entry	Name	Structure
5	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
6	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
7	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
8	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	
9	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
10	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

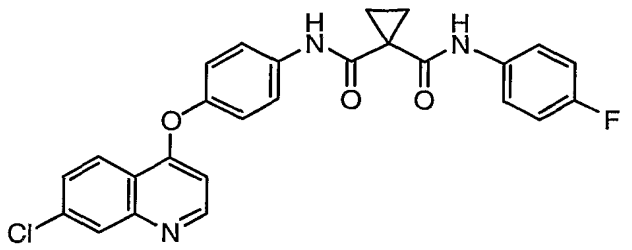
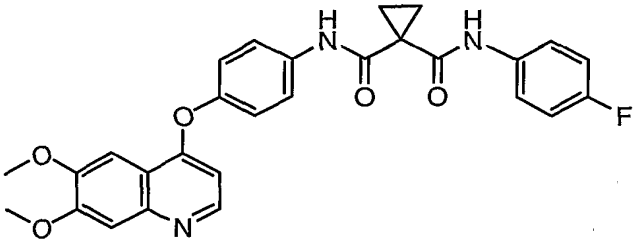
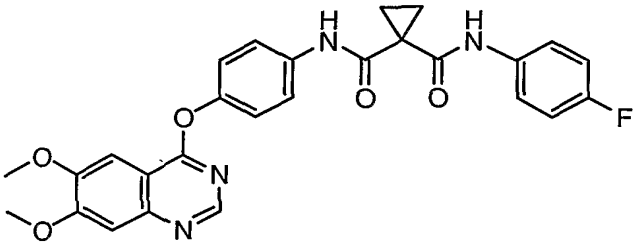
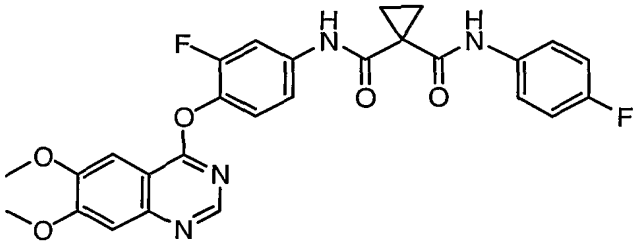
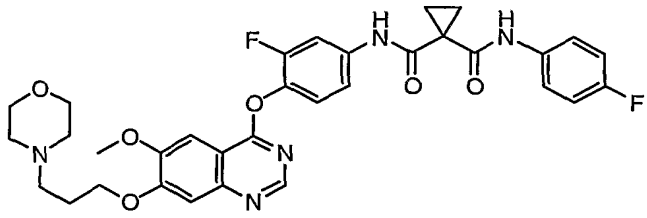
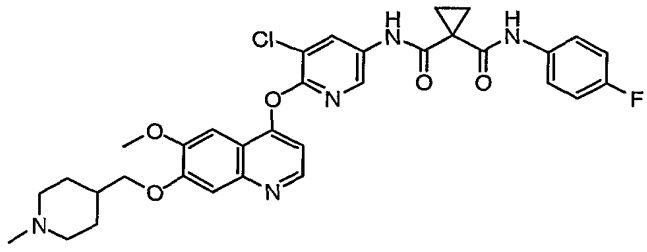
Entry	Name	Structure
11	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
13	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
14	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
15	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
16	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

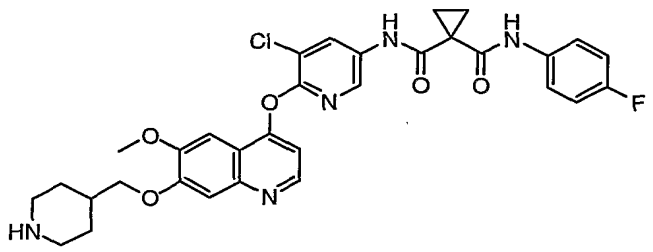
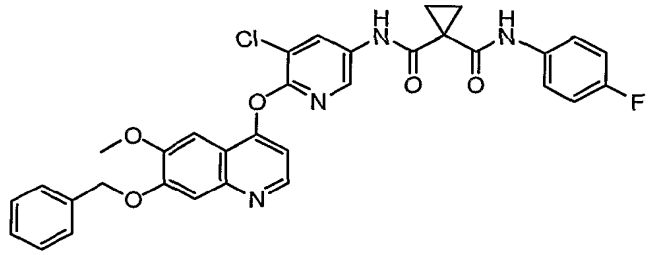
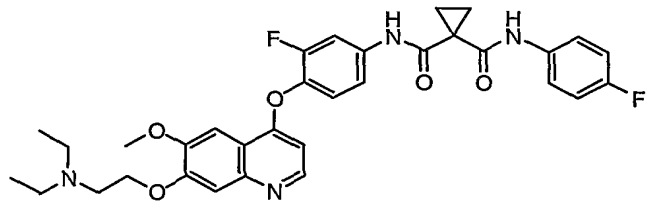
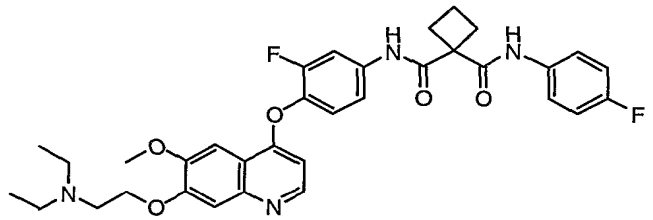
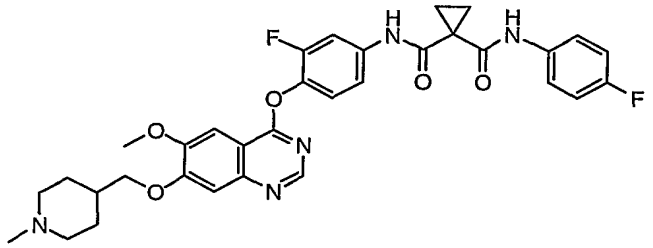
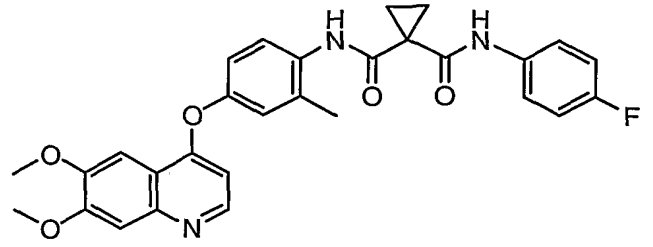
Entry	Name	Structure
17	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
18	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
19	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
20	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
21	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
22	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

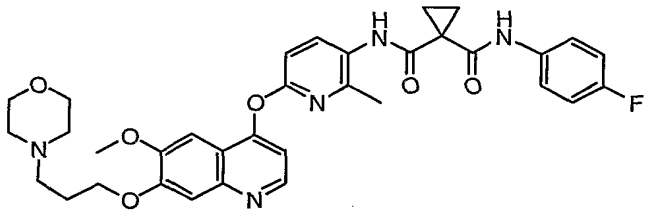
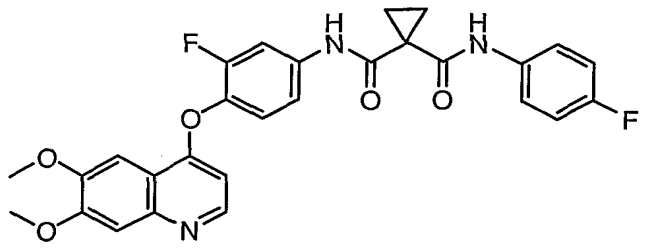
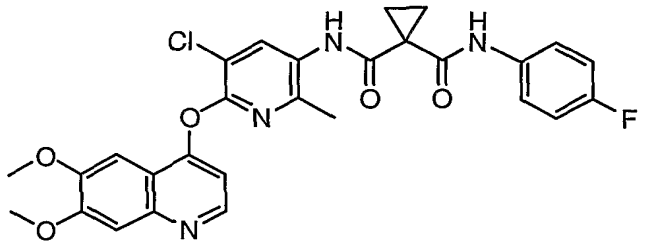
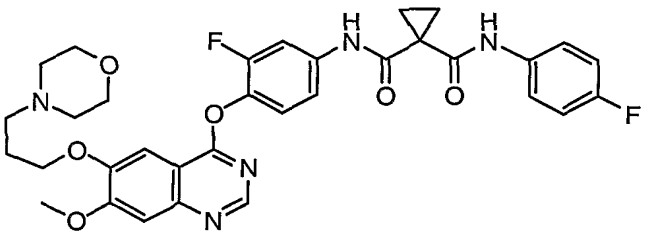
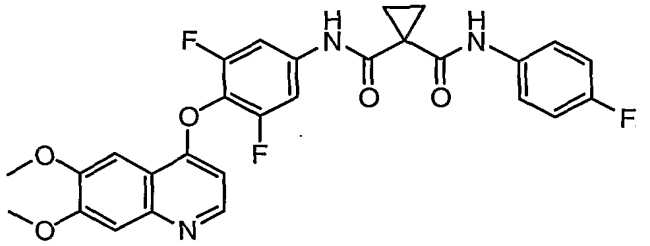
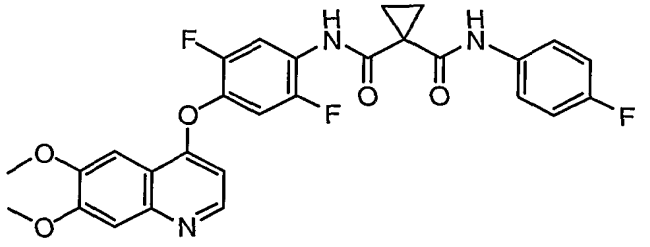
Entry	Name	Structure
23	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	
24	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
25	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
26	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
27	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
28	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

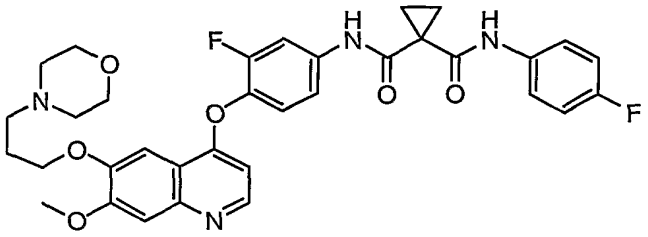
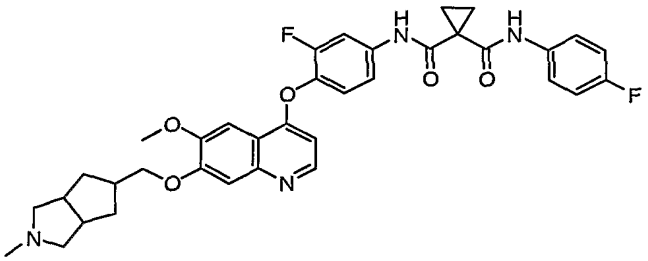
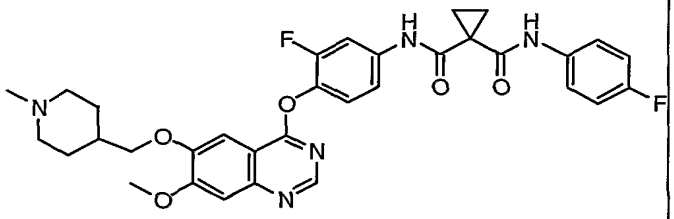
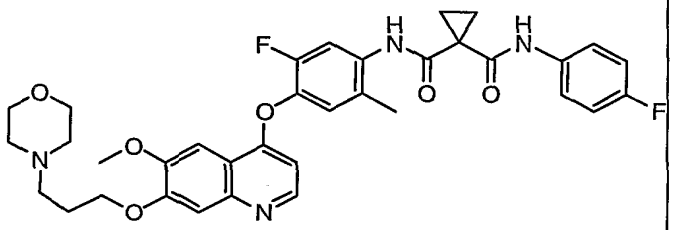
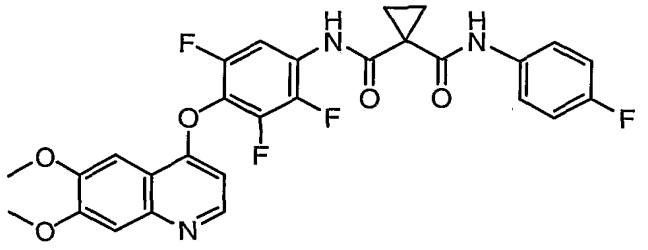
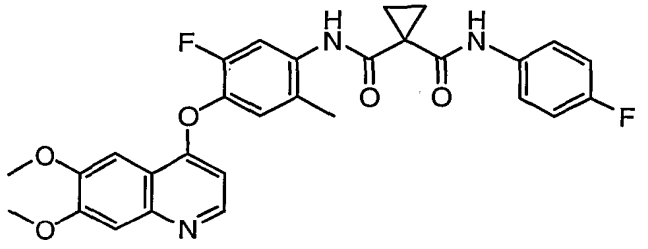
Entry	Name	Structure
29	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
30	N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
31	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
32	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
33	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
34	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

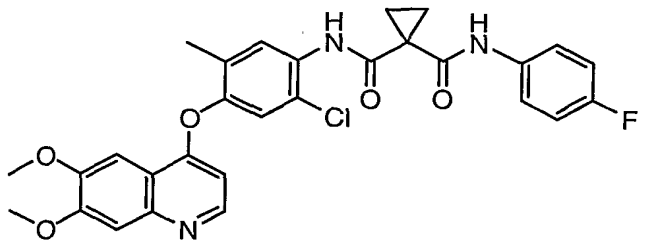
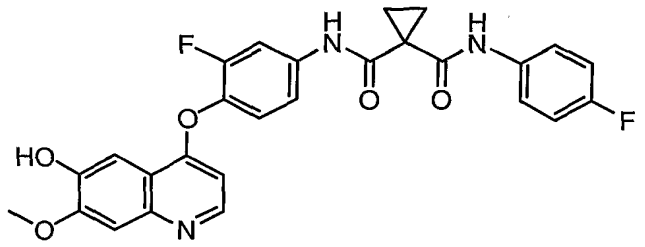
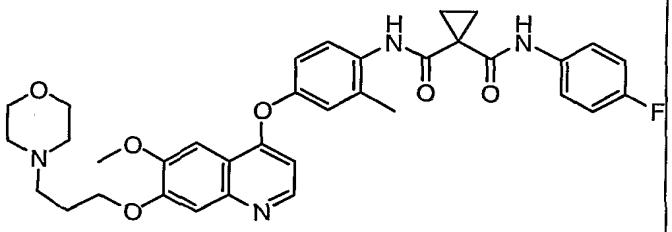
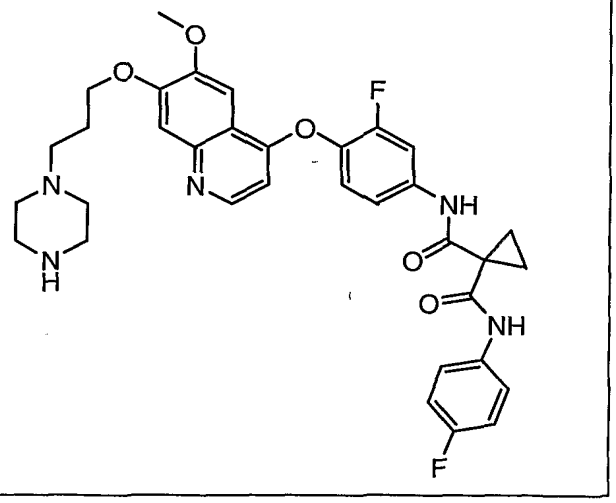
Entry	Name	Structure
35	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
36	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
37	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	
38	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

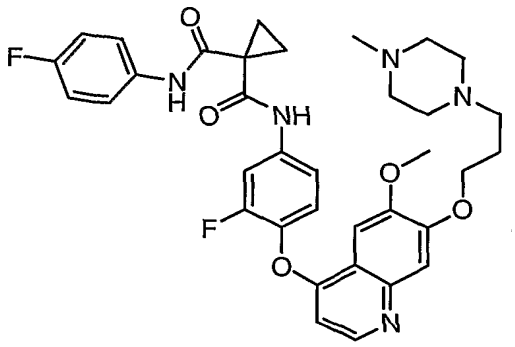
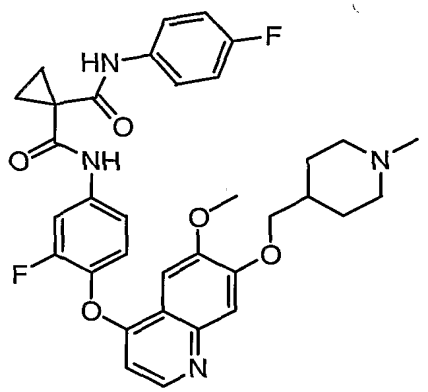
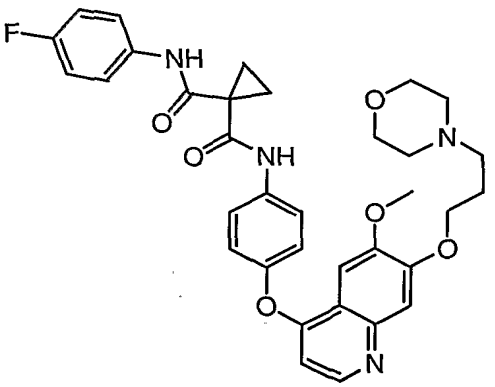
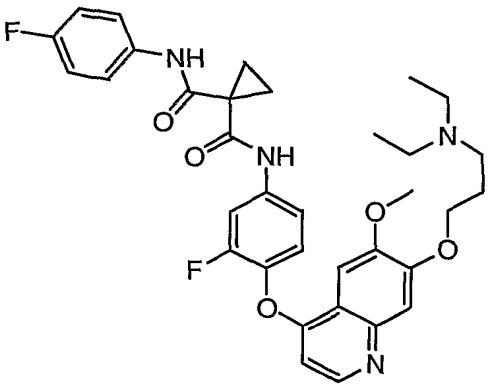
Entry	Name	Structure
39	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
40	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
41	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	
42	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

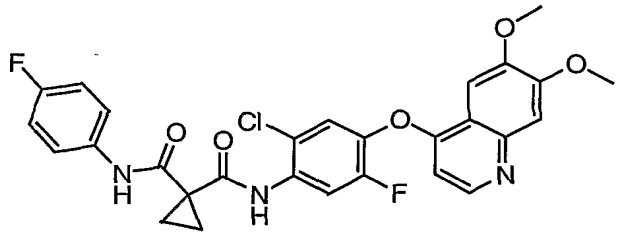
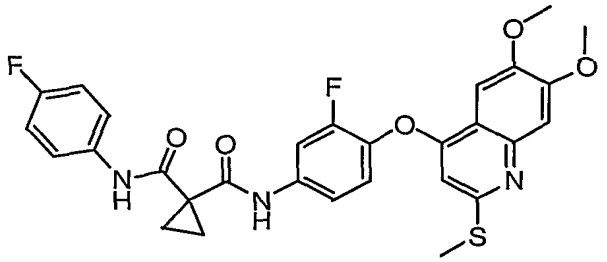
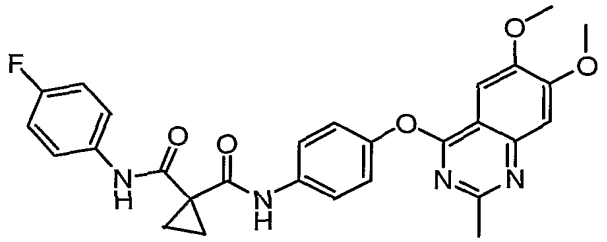
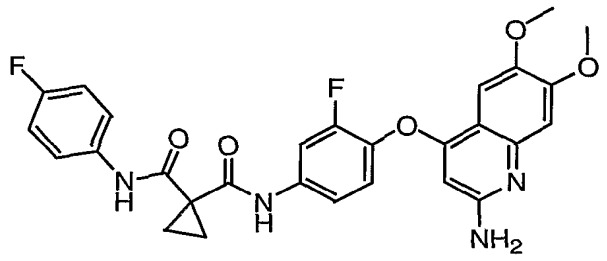
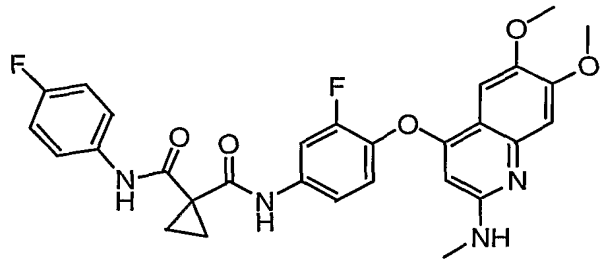
Entry	Name	Structure
43	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
44	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
45	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	
46	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
47	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

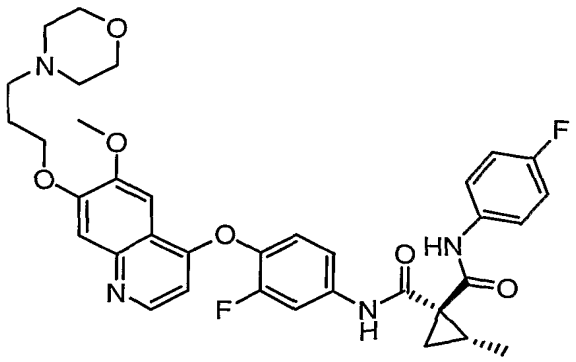
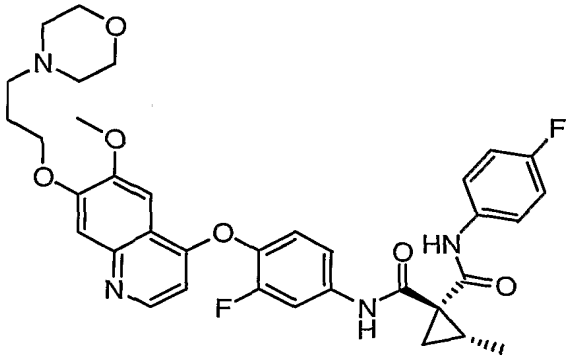
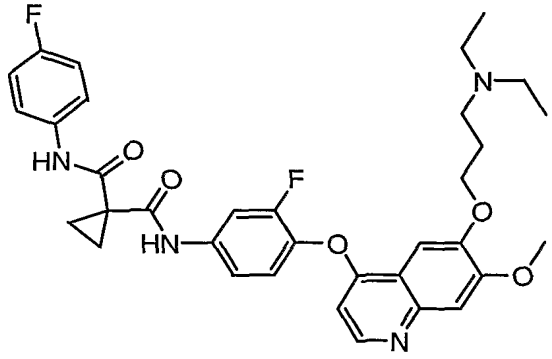
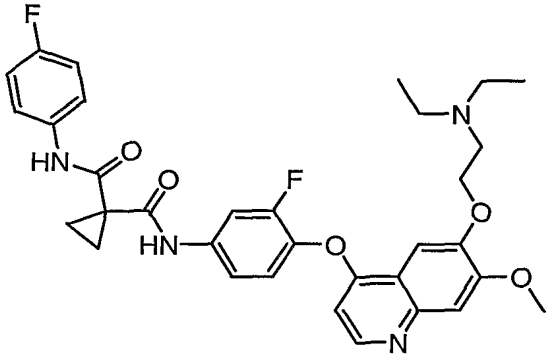
Entry	Name	Structure
48	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
49	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
50	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
51	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

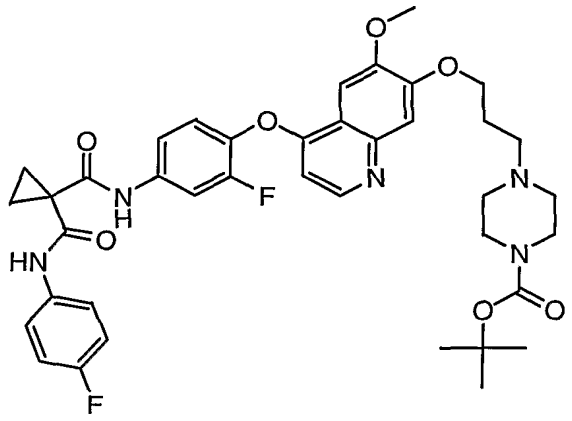
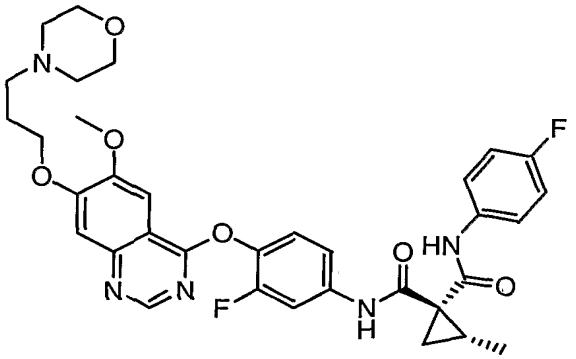
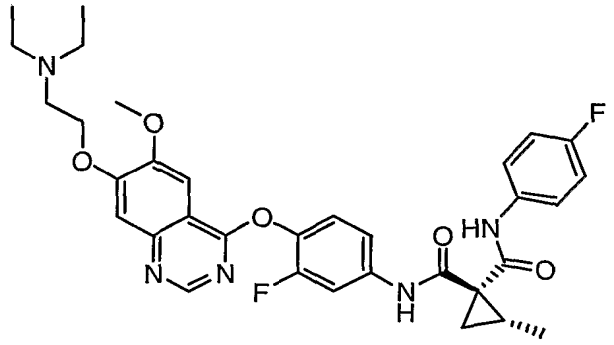
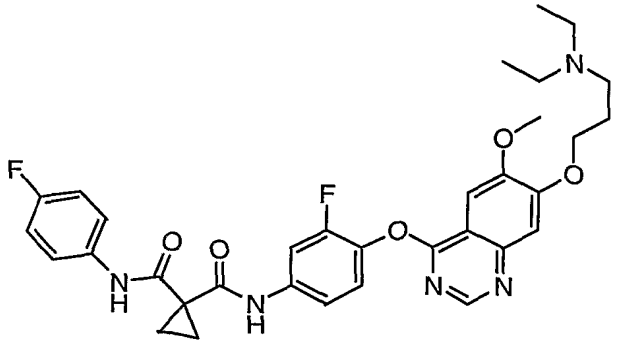
Entry	Name	Structure
52	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	
53	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
54	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
55	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

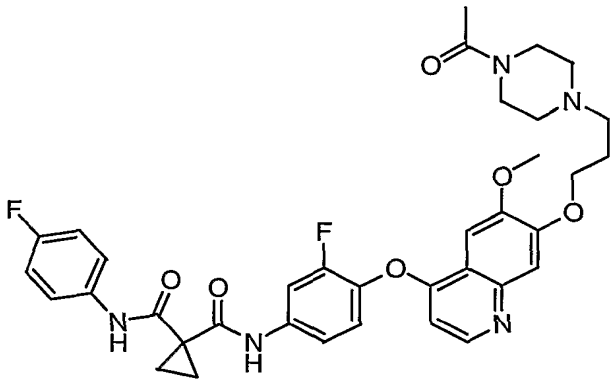
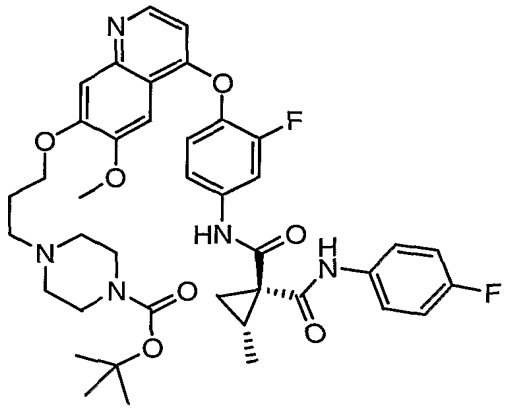
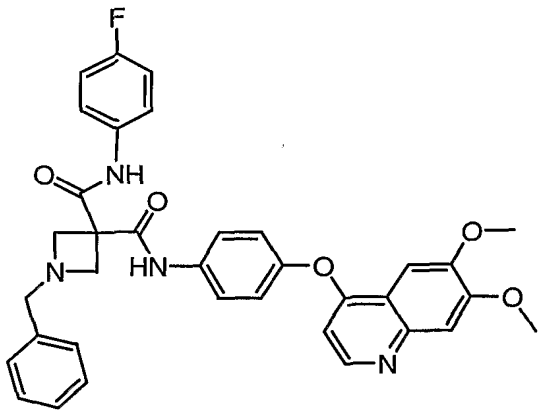
Entry	Name	Structure
56	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
57	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	
58	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	

Table 2

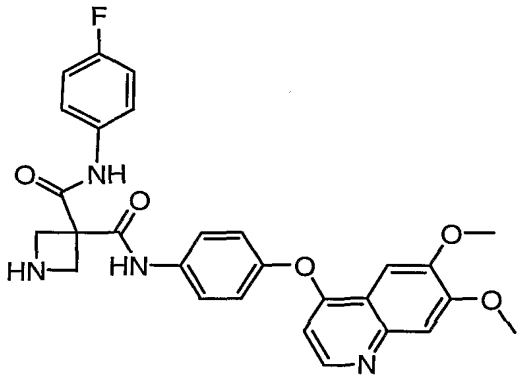
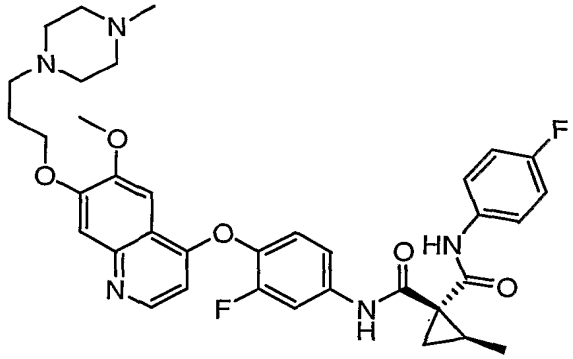
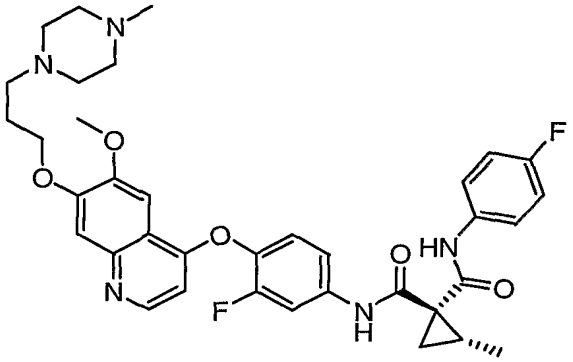
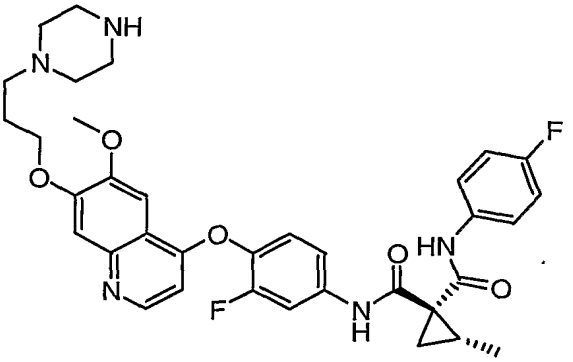
Entry	Name	Structure
59	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	
60	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
61	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
62	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

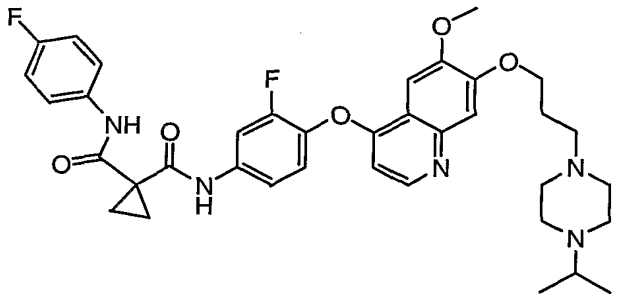
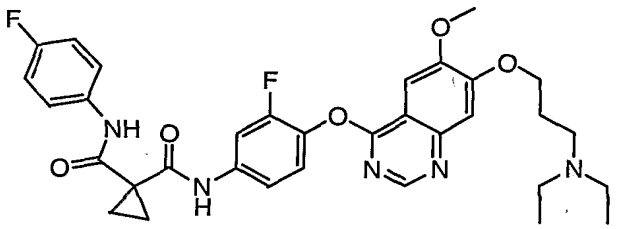
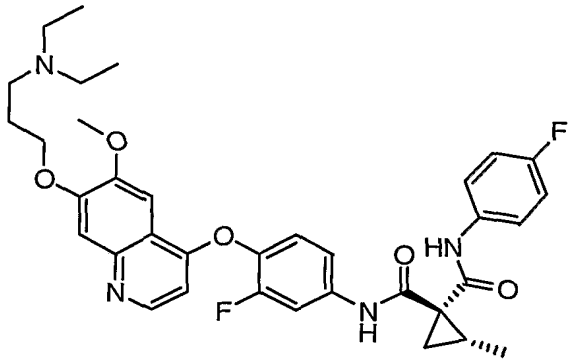
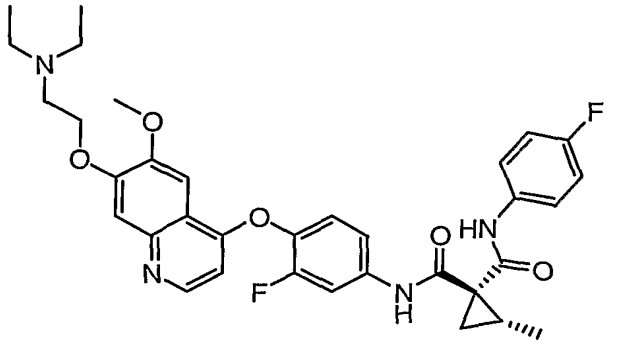
Entry	Name	Structure
63	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
64	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
65	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
66	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

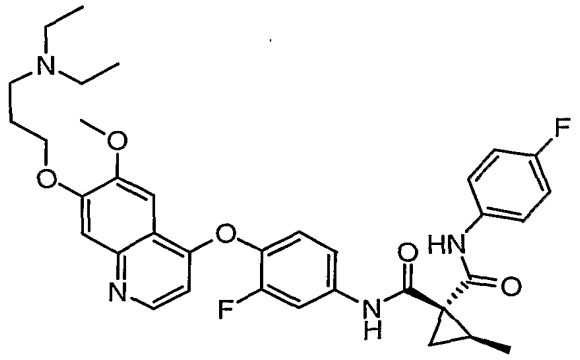
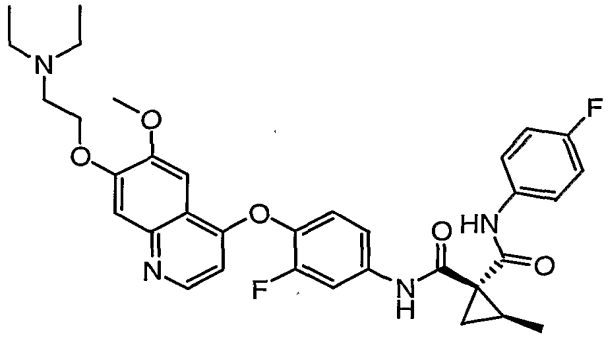
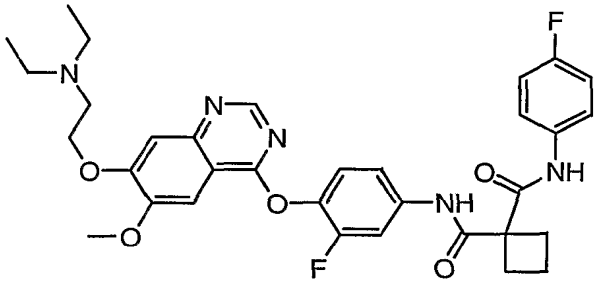
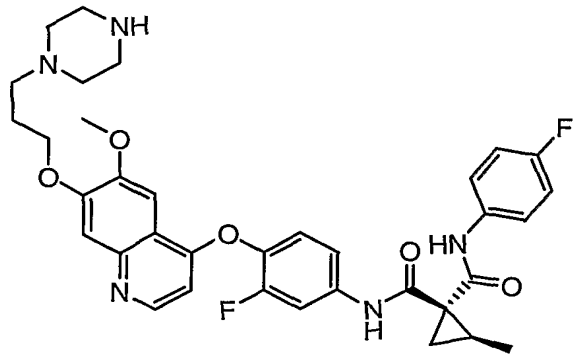
Entry	Name	Structure
67	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
68	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
69	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
70	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

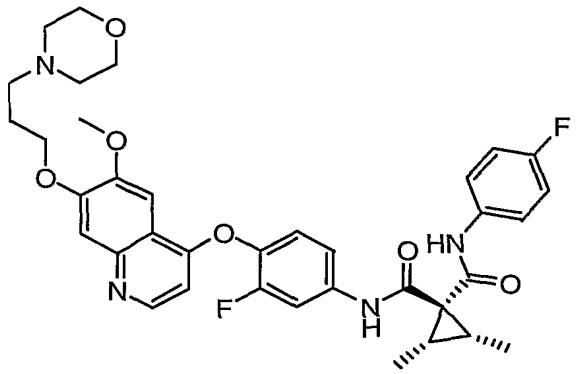
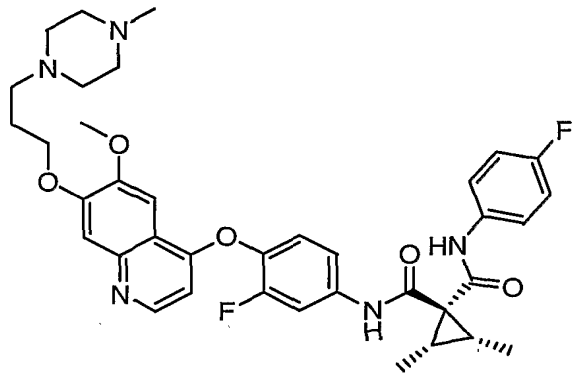
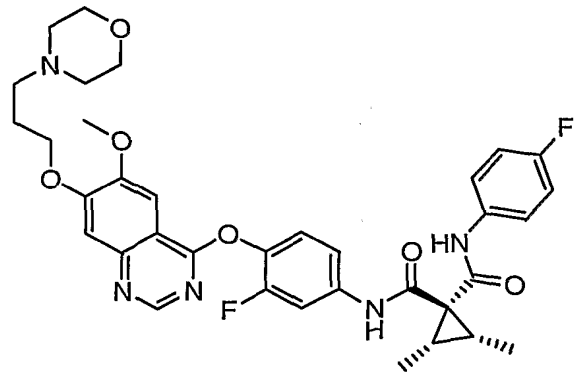
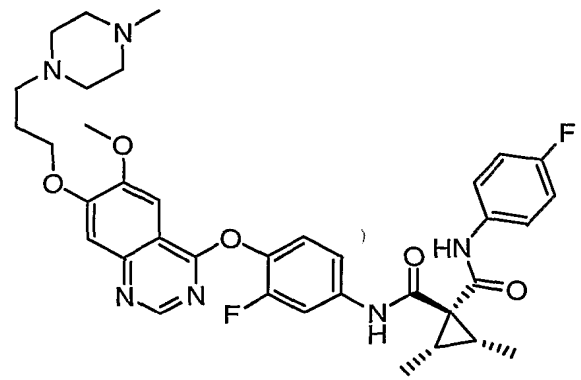
Entry	Name	Structure
71	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
72	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
73	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
74	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

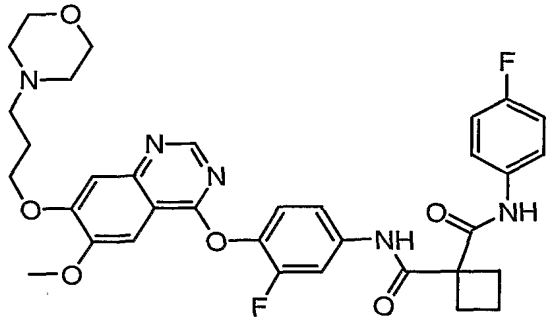
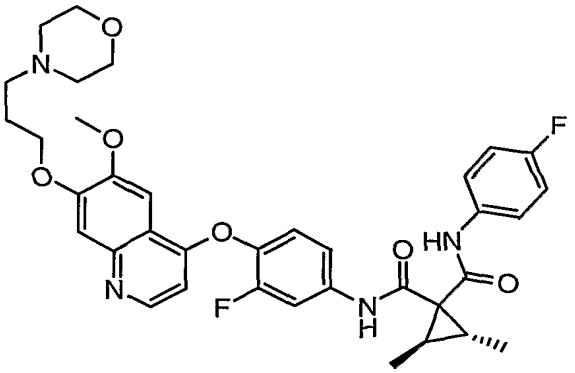
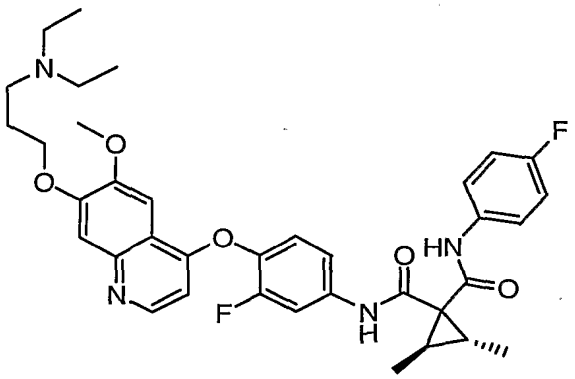
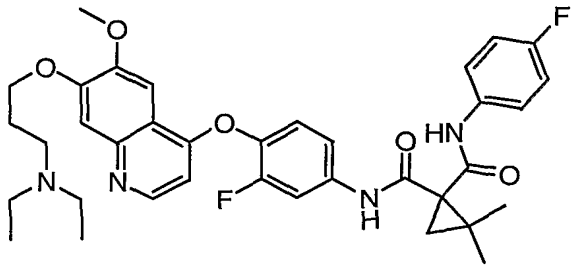
Entry	Name	Structure
75	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
76	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
77	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
78	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

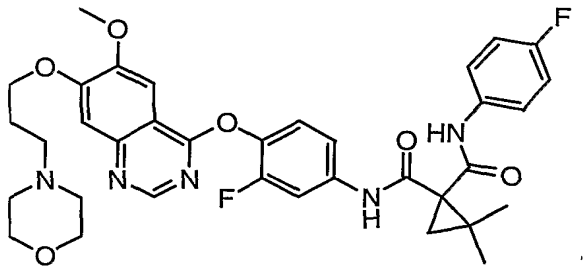
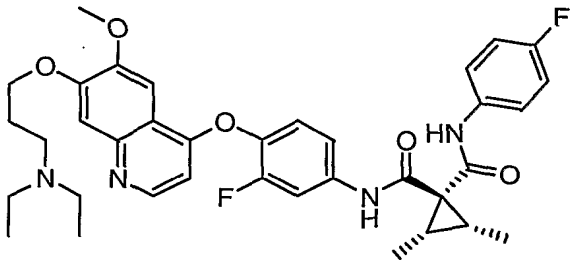
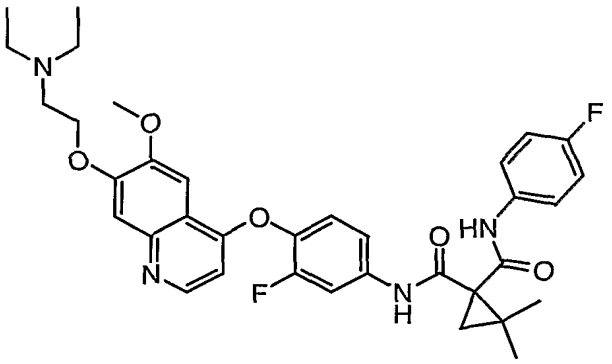
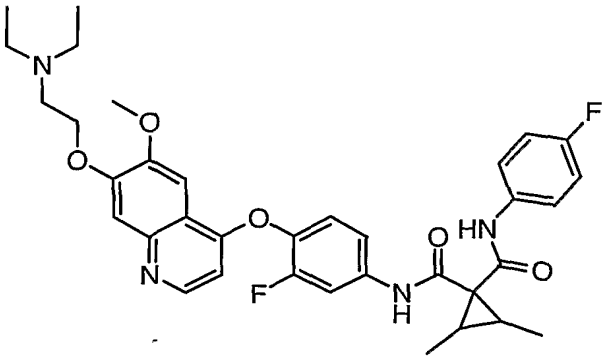
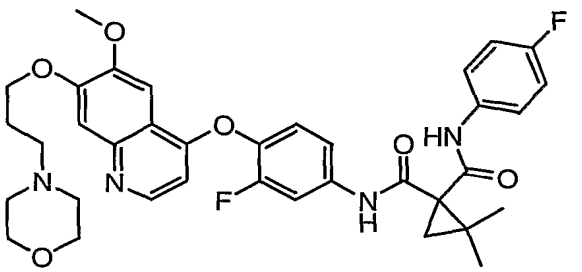
Entry	Name	Structure
79	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
80	(1R,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
81	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
82	(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
83	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

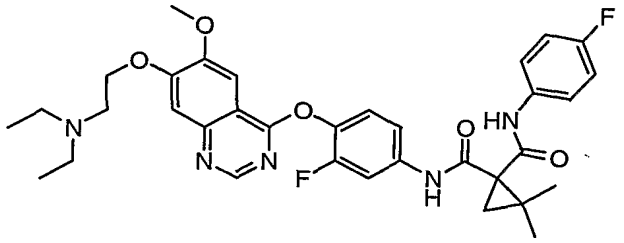
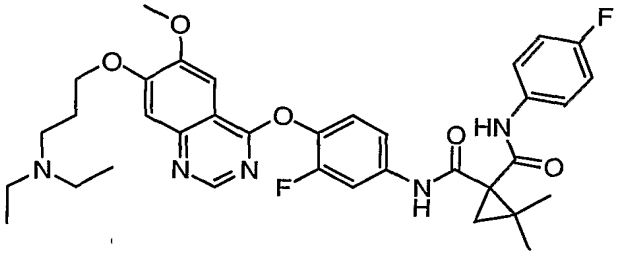
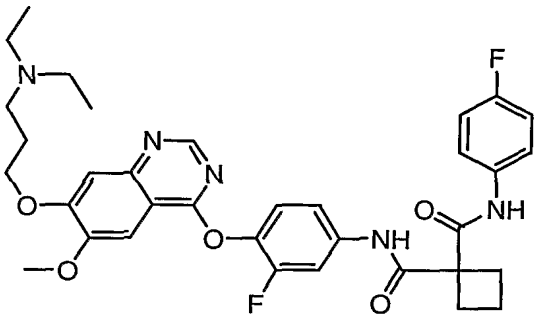
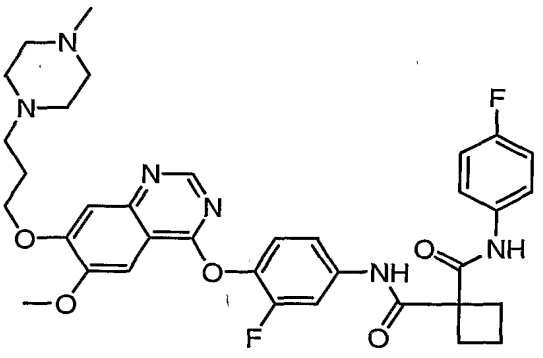
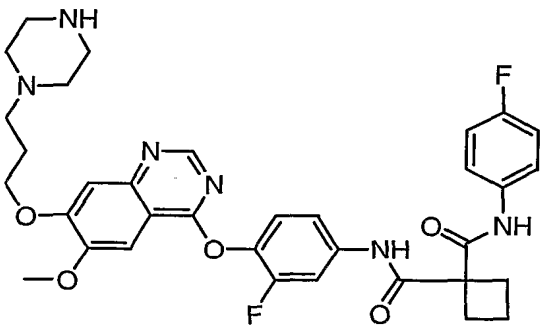
Entry	Name	Structure
84	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
85	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
86	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
87	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
88	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	

Table 2

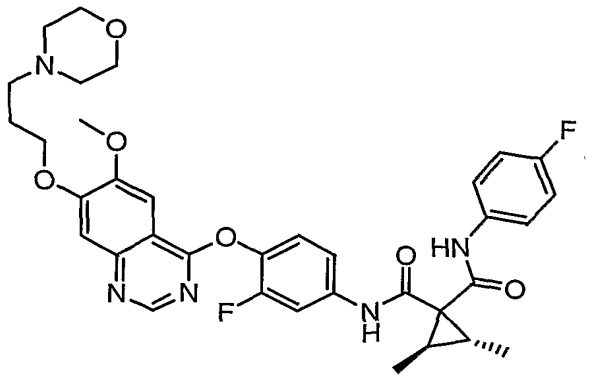
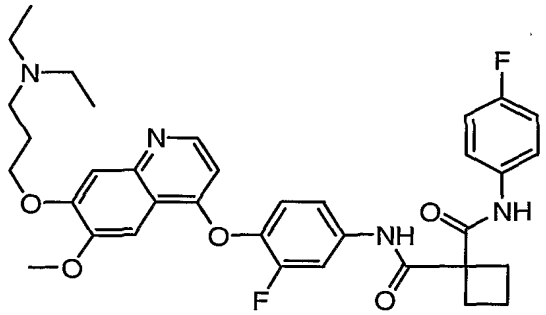
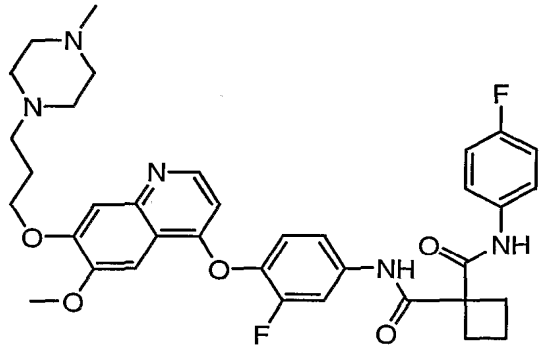
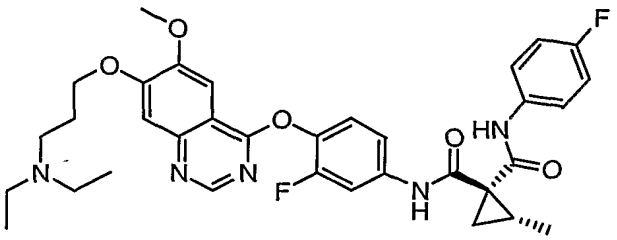
Entry	Name	Structure
89	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
90	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
91	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
92	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

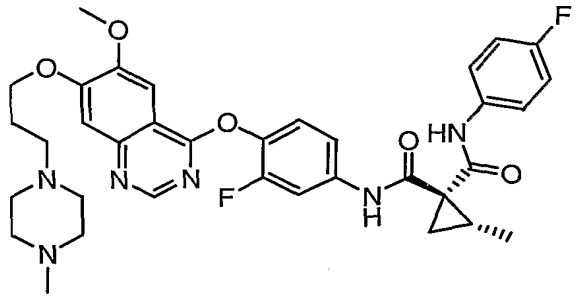
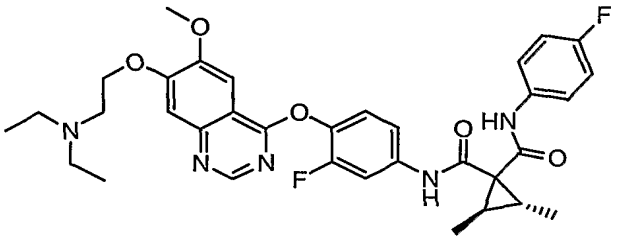
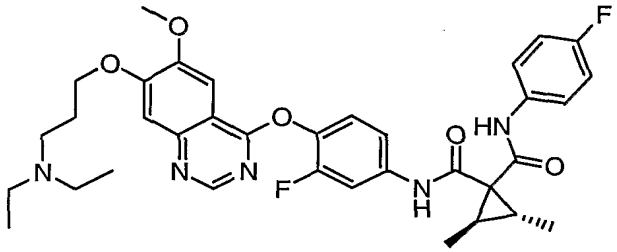
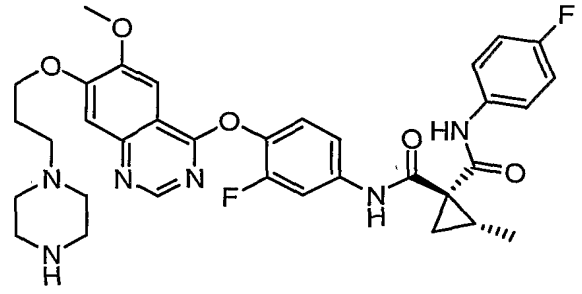
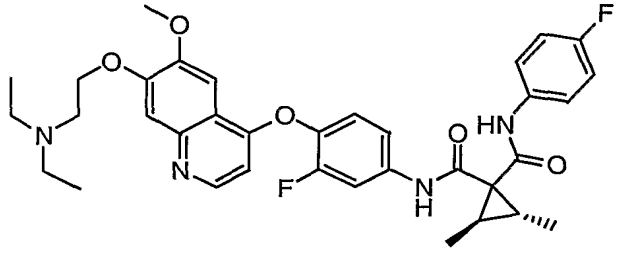
Entry	Name	Structure
93	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
94	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
95	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
96	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
97	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

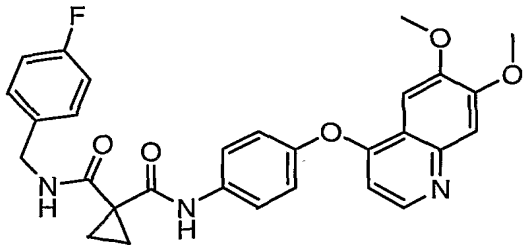
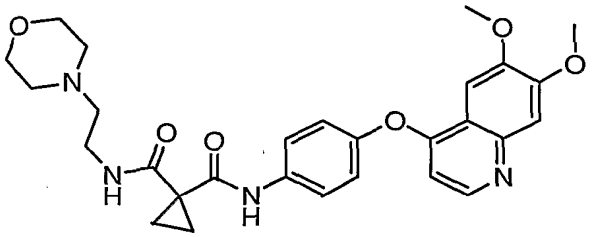
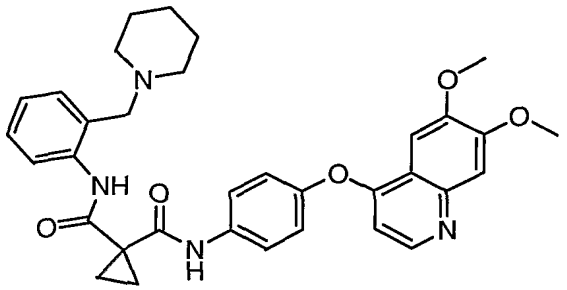
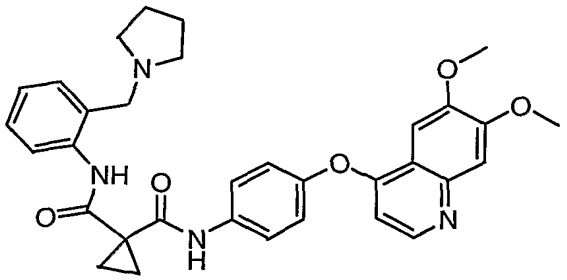
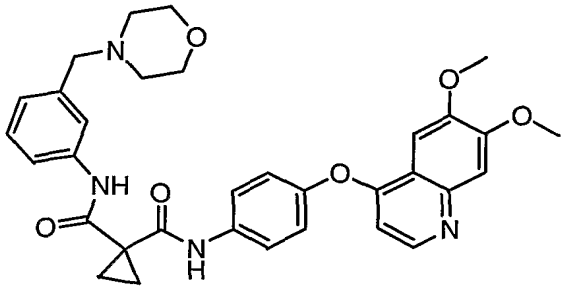
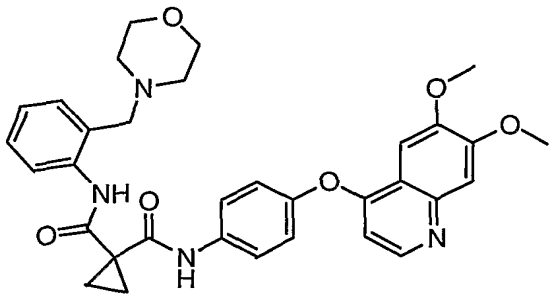
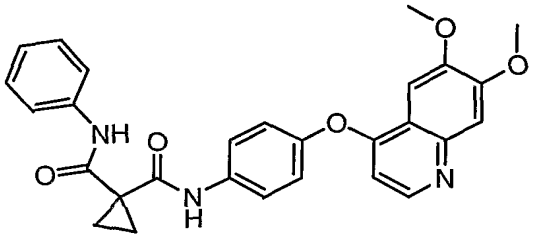
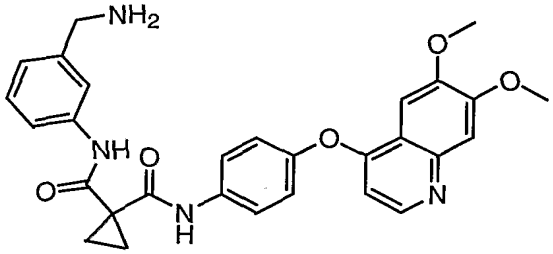
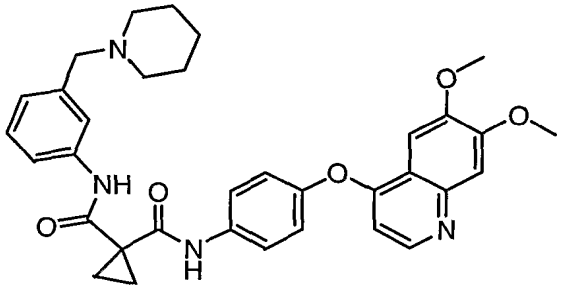
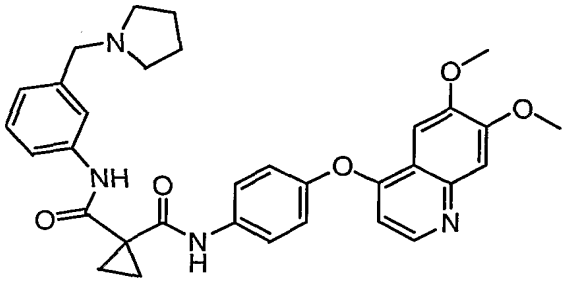
Entry	Name	Structure
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	
99	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	
100	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
101	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
102	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

Table 2

Entry	Name	Structure
103	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
104	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	
105	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	
106	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
107	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

[0176] Another aspect of the invention is a pharmaceutical composition comprising a compound according to any one of paragraphs [0033]-[0120] and a pharmaceutically acceptable carrier.

[0177] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any one of paragraphs [0022]-[0122].

[0178] Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the compound or the pharmaceutical composition according to any of paragraphs [0033]-[0121].

[0179] Another aspect of the invention is the method according to paragraph [0123], wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

[0180] Another aspect of the invention is the method according to paragraph [0124], wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

[0181] Another aspect of the invention is the method according to paragraph [0125], wherein the kinase is c-Met.

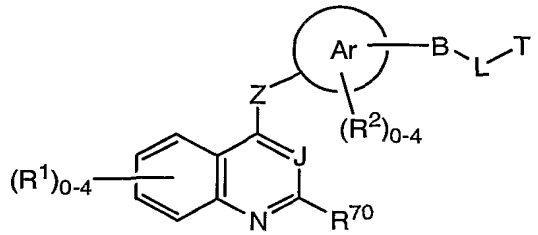
[0182] Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of the compound or the pharmaceutical composition as described in any one of paragraphs [0033]-[0121].

[0183] Another aspect of the invention is a method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, c-Kit, flt-3, and flt-4, the method comprising combining a compound according to any one of paragraphs [0033]-[0120], and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

[0184] Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound according any one of paragraphs [0033]-[0120] to a cell or a plurality of cells.

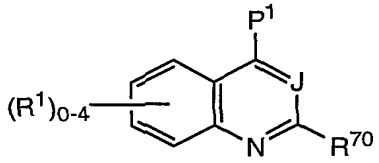
[0185] As mentioned, although improved quinolines and quinazolines of the invention can be made via conventional serial methods, due to their complex structure, more efficient

routes are desirable, particularly convergent syntheses. Thus, the present invention also comprises a process for preparing a compound of Formula **XXI**,

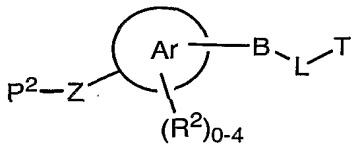


XXI

comprising reaction of a compound of Formula **XXII**, with a compound of Formula **XXIII**



XXII



XXIII

wherein,

each R^1 is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted C_{1-6}alkyl;

R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted C_{1-6}alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}-$, -O-, and $-NR^5-$;

each R^5 is independently selected from -H, optionally substituted C_{1-6}alkyl, optionally substituted aryl, and optionally substituted aryl C_{1-6}alkyl;

Ar is either a five- to ten-membered arylene or a five- to ten-membered heteroarylene containing between one and three heteroatoms;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

each R^3 is independently selected from -H, $-Si(R^5)(R^5)R^5$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two R^3, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, -C(=O)-, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

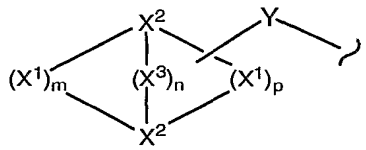
Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}alkyl$, optionally substituted aryl, optionally substituted aryl $C_{1-6}alkyl$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}alkyl$;

two of R^{20}, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to Q or fused to Q;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

R^{50} is either R^3, or according to formula **XXIV**;



XXIV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted C_{1-6}alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a C_{1-6}lkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted C_{1-6}alkyl;

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted C_{1-6}alkyl, optionally substituted heteroalicyclyl C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

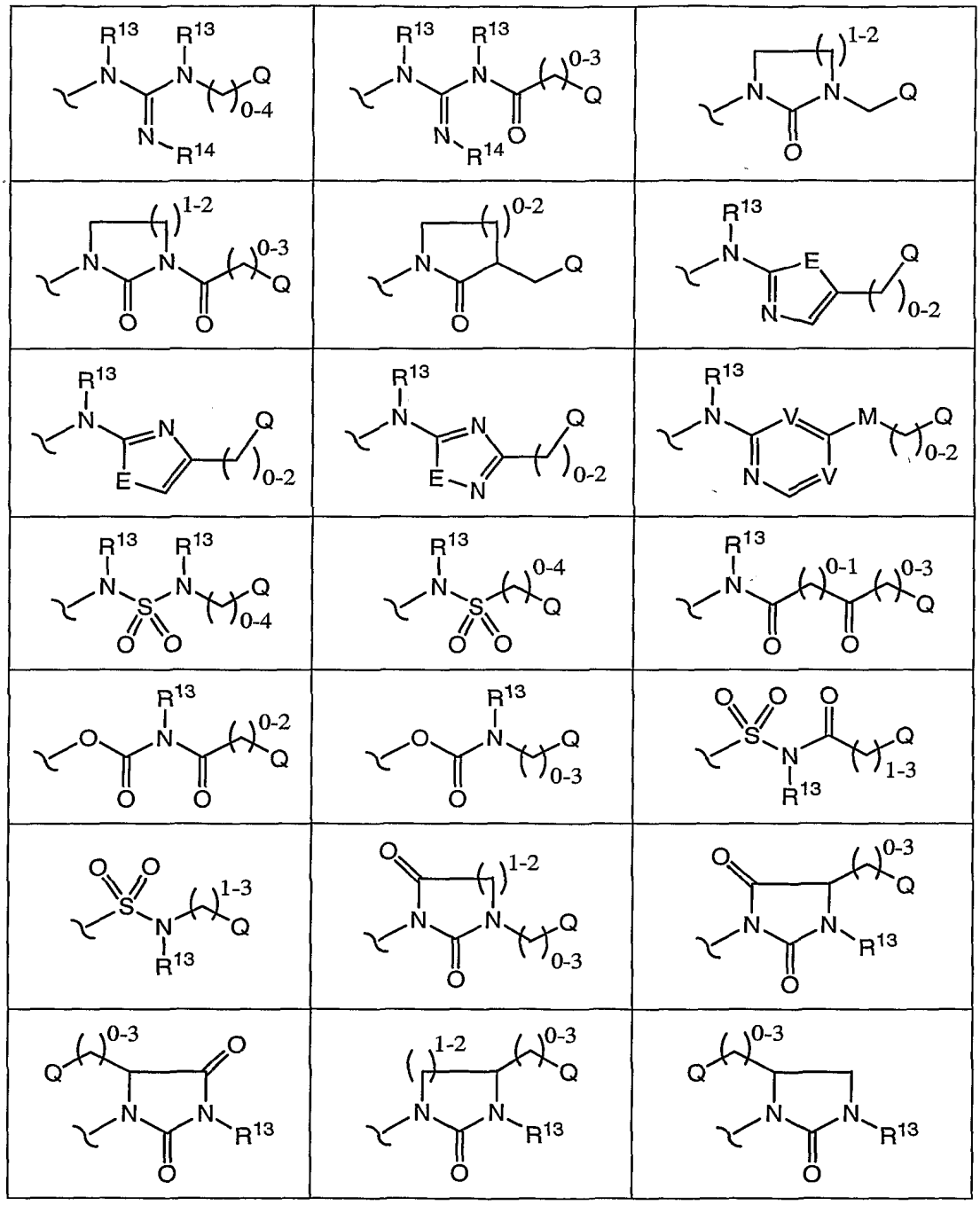
P^1 is a suitable leaving group; and

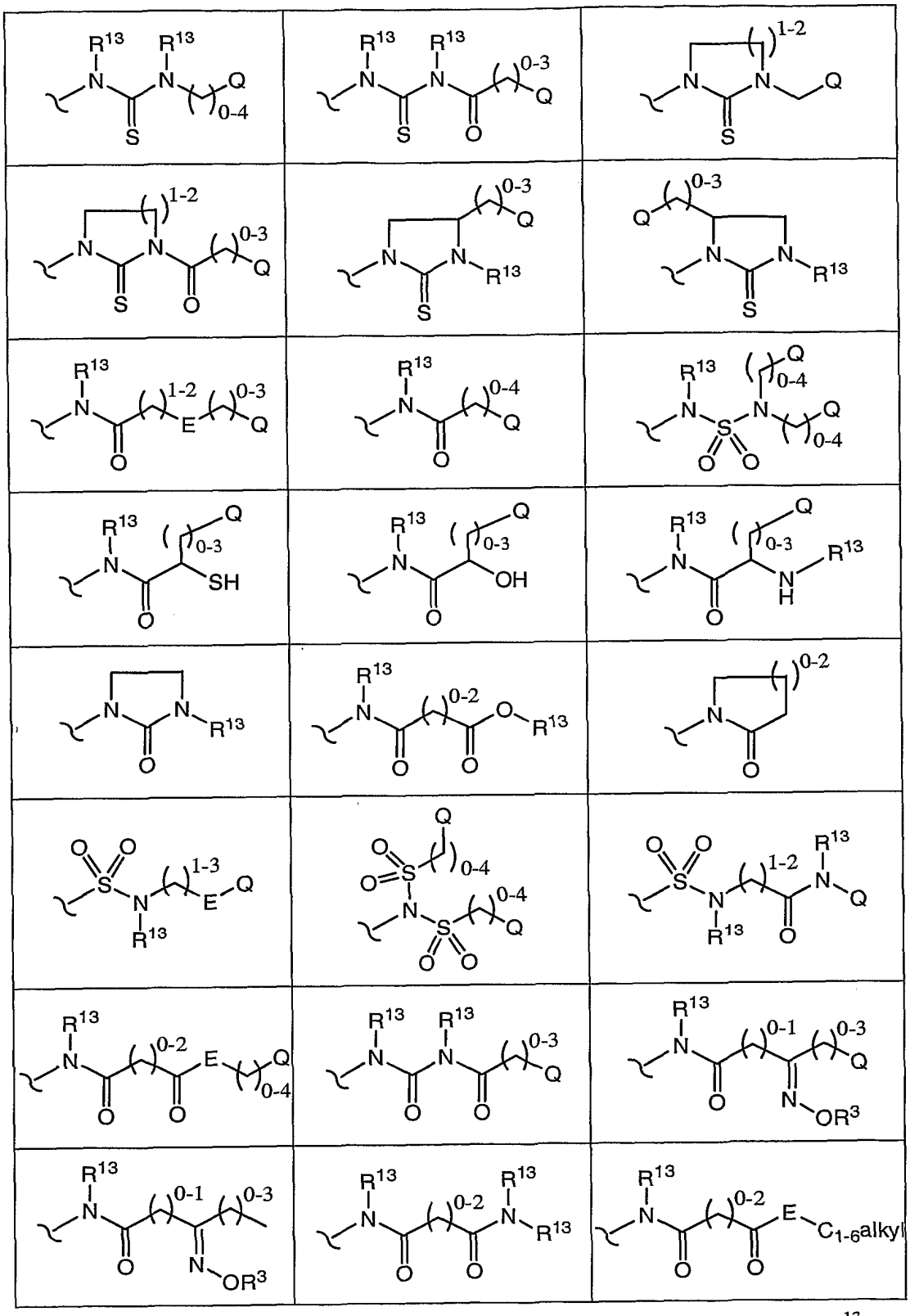
P^2 is selected from -H, a metal, and a group removed *in-situ* when combining **XXII** and **XXIII** to make **XXI**.

[0131] In one example, the process is according to paragraph [0130], wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T about said phenylene.

[0132] In another example, the process is according to paragraph [0131], wherein Z is either -O- or $-NR^5-$.

[0133] In another example, the process is according to paragraph [0132], wherein -B-L-T is selected from the following:





wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2, and -$S(O)_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is

independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of R^{25} on a single carbon can be oxo.

[0134] In another example, the process is according to paragraph [0133], wherein there is one of R^1 that is -D-R^{50} and another of R^1 that is -OR^{3a}.

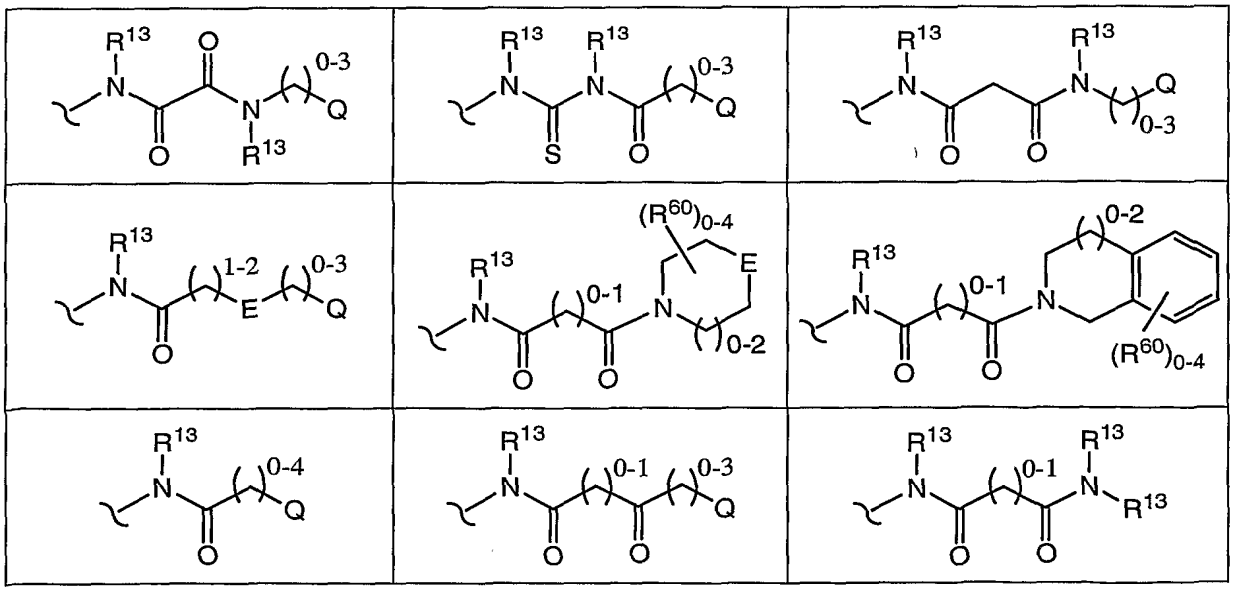
[0135] In another example, the process is according to paragraph [0134], wherein D is -O-.

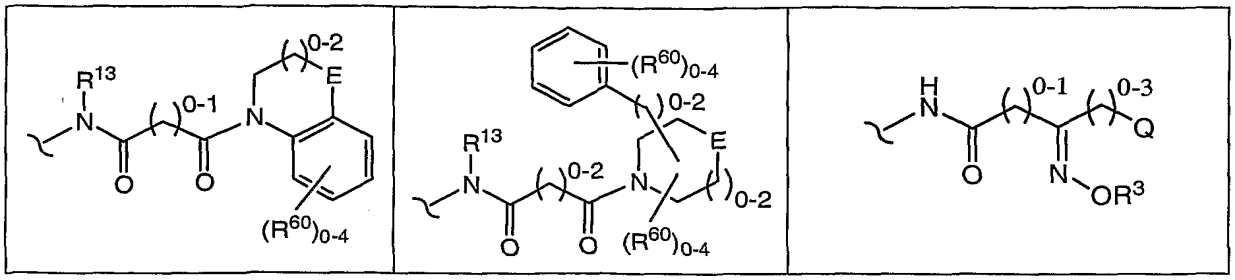
[0136] In another example, the process is according to paragraph [0135], wherein -O-R^{50} and -OR^{3a} are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula **XXI**.

[0137] In another example, the process is according to paragraph [0136], wherein -OR^{3a} is selected from -OH, -$OSi(R^5)(R^5)R^5$, and optionally substituted -OC_{1-6}alkyl.

[0138] In another example, the process is according to paragraph [0137], wherein J is =N- or =C(H)-.

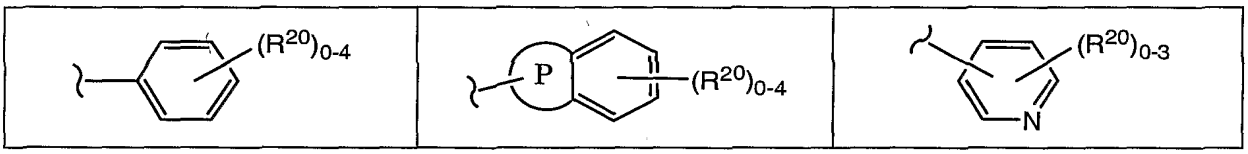
[0139] In another example, the process is according to paragraph [0138], wherein -B-L-T is selected from:





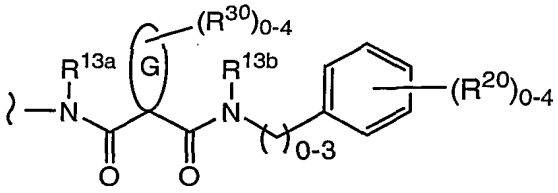
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

[0140] In another example, the process is according to paragraph [0139], wherein Q is selected from the following three formula:

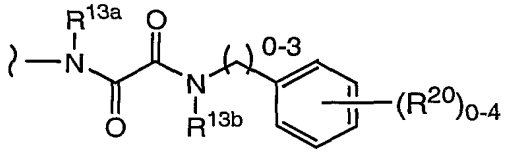


wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

[0141] In another example, the process is according to paragraph [0140], wherein -B-L-T is either of formula **XXV** or formula **XXVI**,



XXV

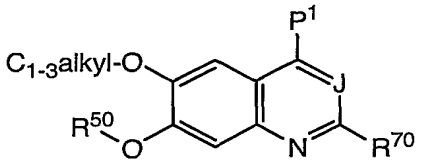


XXVI

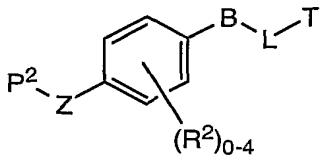
wherein R^{20} is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally

substituted C_{1-6}alkyl; and R^{3a} and R^{3b} are each independently selected from -H and optionally substituted C_{1-6}alkyl.

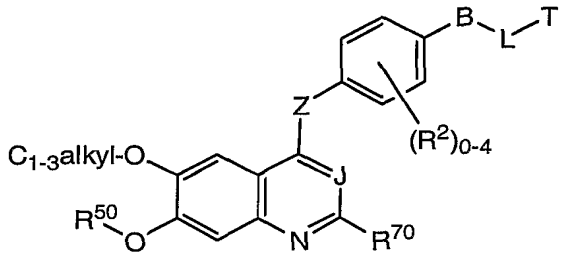
[0142] In another example, the process is according to paragraph [0141], wherein a compound of formula **XXIIa** is combined with a compound of formula **XXIIIa** to make a compound of formula **XXIa**,



XXIIa



XXIIIa



XXIa

wherein -B-L-T, Z, J, R^{50}, and R^2 are as defined above; R^{70} is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that R^5 is selected from -H, C_{1-3}alkyl, and aryl C_{1-3}alkyl; P^1 is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and P^2 is selected from -H and a metal.

[0143] In another example, the process is according to paragraph [0142], wherein P^2 is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

[0144] In another example, the process is according to paragraph [0143], wherein Z is -O-.

[0145] In another example, the process is according to paragraph [0144], wherein P^1 is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

[0146] In another example, the process is according to paragraph [0145], wherein R^{70} is -H.

[0147] In another example, the process is according to paragraph [0146], wherein J is =C(H)-.

[0148] In another example, the process is according to paragraph [0147], wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[0149] In another example, the process is according to paragraph [0148], wherein **XXIIa** and **XXIIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **XXIa**.

[0150] In another example, the process is according to paragraph [0149], wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

[0151] In another example, the process is according to paragraph [0150], wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

[0152] In another example, the process is according to paragraph [0151], wherein **XXIIa** and **XXIIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **XXIa**.

[0153] In another example, the process is according to paragraph [0152], wherein the solvent is an organic solvent.

[0154] In another example, the process is according to paragraph [0153], wherein one molar equivalent of **XXIIa** is combined with between about one quarter and four molar equivalents of **XXIIIa**.

[0155] In another example, the process is according to paragraph [0154], wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **XXIIIa**.

[0156] In another example, the process is according to paragraph [0155], wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

[0157] In another example, the process is according to paragraph [0156], wherein the aromatic solvent is an optionally substituted benzene.

[0158] In another example, the process is according to paragraph [0157], wherein the aromatic solvent is bromobenzene.

[0159] In another example, the process is according to paragraph [0158], wherein the base is 4-N,N-dimethylaminopyridine.

[0160] In another example, the process is according to paragraph [0159], wherein said mixture is heated to reflux for between about three and seven hours.

[0161] In another example, the process is according to paragraph [0160], wherein said mixture is heated to reflux for between about four and six hours.

[0162] In another example, the process is according to paragraph [0155], wherein **XXIIa** is combined with **XXIIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **XXIa**.

[0163] In another example, the process is according to paragraph [0162], wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

[0164] In another example, the process is according to paragraph [0163], wherein the non-aromatic solvent is N,N-dimethylacetamide.

[0165] In another example, the process is according to paragraph [0164], wherein the base is potassium carbonate.

[0166] In another example, the process is according to paragraph [0165], wherein said mixture is heated to about 50°C between about ten and twenty hours.

[0167] In another example, the process is according to paragraph [0166], wherein the aromatic solvent is an optionally substituted pyridine.

[0168] In another example, the process is according to paragraph [0167], wherein the aromatic solvent is 2,6-lutidine.

[0169] In another example, the process is according to paragraph [0168], wherein the base is 2,6-lutidine.

[0170] In another example, the process is according to paragraph [0169], wherein said mixture is heated to reflux for between about three and seven hours.

[0171] In another example, the process is according to paragraph [0170], wherein said mixture is heated to reflux for between about four and six hours.

[0172] In another example, the process is according to paragraph [0154], wherein one molar equivalent of **XXIIIa** is combined with more than one but less than two molar equivalents of **XXIIa**.

[0173] In another example, the process is according to paragraph [0172], wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **XXIa**.

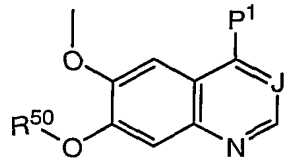
[0174] In another example, the process is according to paragraph [0173], wherein the aromatic solvent is an optionally substituted pyridine.

[0175] In another example, the process is according to paragraph [0174], wherein the aromatic solvent is 2,6-lutidine.

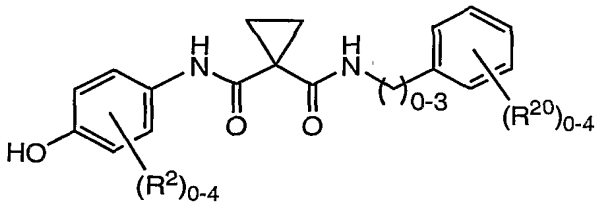
[0176] In another example, the process is according to paragraph [0175], wherein the base is 2,6-lutidine.

[0177] In another example, the process is according to paragraph [0176], wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

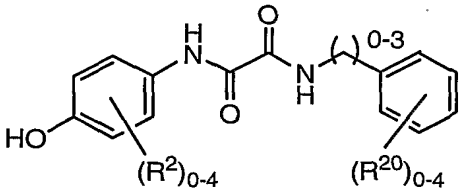
[0178] In another example, the process is according to any of paragraphs [0149] – [0177], wherein a compound of formula **XXIIb** is substituted for the compound of formula **XXIIa**, and either a compound of formula **XXIIIb** or a compound of formula **XXIIIc** is substituted for the compound of formula **XXIIIa**, in order to make a compound of formula **XXIb** or a compound of formula **XXIc**, respectively,



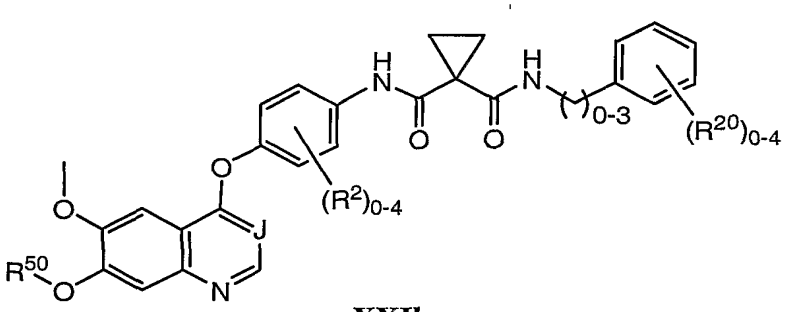
XXIIb



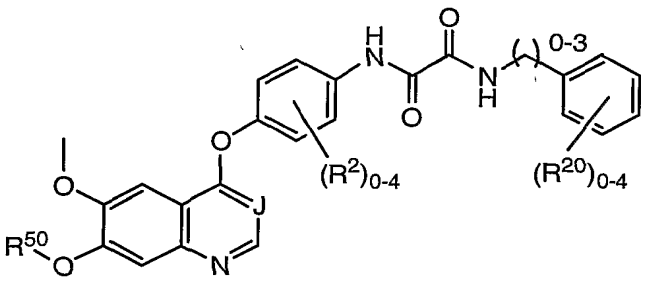
XXIIIb



XXIIIc



XXIb



XXIc

wherein J, R^{50}, R^{20} and R^2 are as defined above.

[0179] In another example, the process is according to paragraph [0178], wherein R^2, if present, is halogen.

[0180] In another example, the process is according to paragraph [0179], wherein R^2, if present, is fluorine.

[0181] In another example, the process is according to paragraph [0180], wherein R^2, if present, is up to two fluorines *ortho* to the oxygen of the phenylene to which R^2 is attached.

[0182] In another example, the process is according to paragraph [0130], used to make a compound listed in either Table 1 or Table 2.

[0183] In another example the process is according to any of paragraphs [0130] - [0182], further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

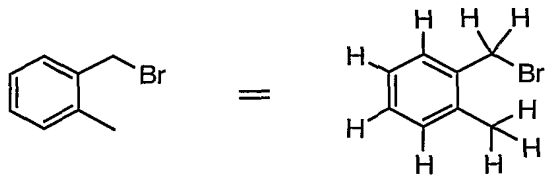
Definitions

[0184] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in

which they are used indicates otherwise or they are expressly defined to mean something different.

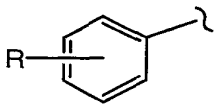
[0185] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond. The symbol "〰" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the "〜" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

[0186] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.



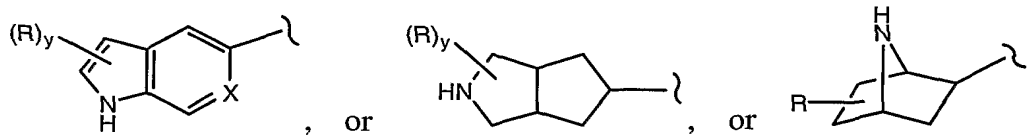
[0187] In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe a "spirocyclyl," then if ring A is cyclopropyl, there are at most four hydrogens on ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

[0188] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



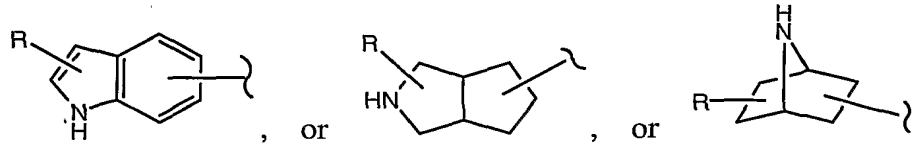
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0189] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



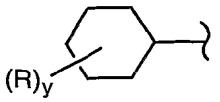
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted (for example the -NH- in the formula above), implied (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0190] When there are more than one such depicted "floating" groups, as for example in the formulae:

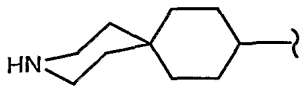


where there are two groups, namely, the "R" and the bond indicating attachment to a parent structure; then, unless otherwise defined, the "floating" groups may reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0191] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0192] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that eight carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, either "butyl" or "C_4 alkyl" is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-yne radicals; and for example, "propyl" or "C_3 alkyl" each include *n*-propyl, propenyl, and isopropyl.

[0193] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene

(-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), dimethylpropylene (-$CH_2C(CH_3)_2CH_2$-), and cyclohexylpropylene (-$CH_2CH_2CH(C_6H_{13})$).

[0194] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[0195] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0196] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0197] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0198] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as -$OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and -$O(CH_2CH_2O)_xCH_3$, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or -$OCH_2(CH_2)_yOH$, where y is for example an

integer of between about one and about ten, in another example y is an integer of between about one and about four.

[0199] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0200] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

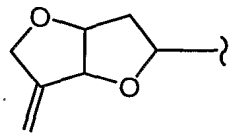
[0201] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

[0202] "Aryl" refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0203] "Arylene" generically refers to any aryl that has at least two groups attached thereto. For a more specific example, "phenylene" refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0204] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to six carbons; this can also be refered to as C_{1-6} arylalkyl.

[0205] "Exo-alkenyl" refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0206] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0207] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0208] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. "Haloalkyl" and "haloaryl" refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, "dihaloaryl," "dihaloalkyl," "trihaloaryl" etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0209] "Heteroarylene" generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, "pyridylene" refers to a divalent pyridyl

ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0210] "Heteroatom" refers to O, S, N, or P.

[0211] "Heterocyclyl" refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0212] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

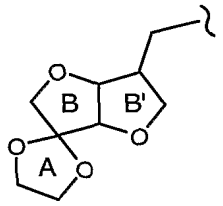
[0213] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

[0214] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to a heterocyclylalkyl where the "alkyl" portion of the group has one to six carbons. "Heteroalicyclylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and "heteroarylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic Such terms may be described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl C_{1-6}alkyl" are equivalent terms.

[0215] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted arylC_{1-8} alkyl," optional substitution may occur on both the "C_{1-8} alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitution are listed below in the definition of "substituted."

[0216] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system."

[0217] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0218] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl), optionally substituted aryl (for example, 4-hydroxyphenyl), optionally substituted arylalkyl (for example, 1-phenyl-ethyl), optionally substituted heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl or 1-methyl-piperidin-4-yl), optionally substituted alkoxy, alkylenedioxy (for example methylenedioxy), optionally substituted amino (for example, alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy), optionally substituted arylalkyloxy (for example, benzyloxy), carboxy (-CO_2H), carboalkoxy (that is, acyloxy or -OC(=O)R), carboxyalkyl (that is, esters or -CO_2R), carboxamido, benzyloxycarbonylamino (CBZ-amino), cyano, acyl, halogen, hydroxy, nitro, sulfanyl, sulfinyl, sulfonyl, thiol, halogen, hydroxy, oxo, carbamyl, acylamino, and sulfonamido.

[0219] "Suitable leaving group" is defined as the term would be understood by one of ordinary skill in the art; that is, a carbon with such a group attached, upon reaction wherein a new bond is to be formed, loses such a group upon formation of the new bond. The invention pertains particularly with respect convergent synthesis, to reactions where such a leaving group is bonded to a reaction partner that is aromatic, undergoes a bond-forming reaction and remains aromatic. A typical example of such a reaction is a nucleophilic aromatic substitution reaction, as would be understood by one of ordinary skill in the art. However, the invention is not limited to such mechanistic restrictions; for example, reactions where there is, for example, an insertion reaction (for example by a transition metal) into the bond between the aromatic reaction partner and its leaving group

followed by reductive coupling can also be used within the scope of the invention. Examples of suitable leaving groups include halogens, optionally substituted aryl or alkyl sulfonates, phosphonates, azides, $RS(O)_{0-2}$- where R is, for example optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0220] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0221] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0222] "Sulfonyl" refers to the groups: $-S(O_2)$-H, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-optionally substituted aryl), $-S(O_2)$-(optionally substituted heterocyclyl), $-S(O_2)$-(optionally substituted alkoxy), $-S(O_2)$-optionally substituted aryloxy), and $-S(O_2)$-(optionally substituted heterocyclyloxy).

[0223] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0224] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0225] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0226] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0227] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0228] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0229] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, -OCH_2-, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted orientation, for example "-OCH_2-" is meant to mean not only "-OCH_2-" as drawn, but also "-CH_2O-."

[0230] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0231] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to

both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0232] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0233] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0234] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0235] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma),

alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma,

dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0236] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0237] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0238] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and

arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0239] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0240] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0241] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0242] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet

been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0243] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular c-Met, c-Kit, KDR, flt-3, or flt-4-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[0244] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0245] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include

administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0246] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[0247] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0248] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form

can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0249] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0250] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0251] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0252] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0253] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0254] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0255] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0256] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0257] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0258] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0259] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0260] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

Utility of compounds of the invention as screening agents

[0261] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example c-Met, KDR, c-Kit, flt-3, or flt-4, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the

compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0262] The determination of the binding of the candidate agent to, for example, c-Met, KDR, c-Kit, flt-3, or flt-4 protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion of the c-Met, KDR, c-Kit, flt-3, or flt-4 protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0263] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0264] In some embodiments, only one of the components is labeled. For example, c-Met, KDR, c-Kit, flt-3, or flt-4 protein may be labeled at tyrosine positions using ^{125}I, or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the candidate agents.

[0265] The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity.

They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to c-Met, KDR, c-Kit, flt-3, or flt-4.

[0266] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 daltons and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0267] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0268] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to c-Met, KDR, c-Kit, flt-3, or flt-4, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the

candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0269] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to for example c-Met, KDR, c-Kit, flt-3, or flt-4 for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C

[0270] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0271] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to c-Met, KDR, c-Kit, flt-3, or flt-4 and thus is capable of binding to, and potentially modulating, the activity of the c-Met, KDR, c-Kit, flt-3, or flt-4. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0272] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to c-Met, KDR, c-Kit, flt-3, or flt-4 with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to c-Met, KDR, c-Kit, flt-3, or flt-4.

[0273] It may be of value to identify the binding site of c-Met, KDR, c-Kit, flt-3, or flt-4. This can be done in a variety of ways. In one embodiment, once c-Met, KDR, c-Kit, flt-3, or flt-4 has been identified as binding to the candidate agent, the c-Met, KDR, c-Kit, flt-3, or flt-4 is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0274] Modulation is tested by screening for candidate agents capable of modulating the activity of c-Met, KDR, c-Kit, flt-3, or flt-4 comprising the steps of combining a candidate agent with c-Met, KDR, c-Kit, flt-3, or flt-4, as above, and determining an alteration in the

biological activity of the c-Met, KDR, c-Kit, flt-3, or flt-4. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphology, and the like.

[0275] Alternatively, differential screening may be used to identify drug candidates that bind to native c-Met, KDR, c-Kit, flt-3, or flt-4, but cannot bind to modified c-Met, KDR, c-Kit, flt-3, or flt-4.

[0276] Positive controls and negative controls may be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

[0277] A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

Abbreviations and their Definitions

[0278] The following abbreviations and terms have the indicated meanings throughout.

Abbreviation	Meaning
Ac	acetyl
ATP	adenosine triphosphate
BNB	4-bromomethyl-3-nitrobenzoic acid
Boc	t-butyloxy carbonyl

Abbreviation	Meaning
br	broad
Bu	butyl
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DBU	Diazabicyclo[5.4.0]undec-7-ere
DCM	dichloromethane = methylene chloride = CH_2Cl_2
DCE	dichloroethylene
DEAD	diethyl azodicarboxylate
DIC	diisopropylcarbodiimide
DIEA	N,N-diisopropylethyl amine
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylfonnamide
DMSO	dimethyl sulfoxide
DVB	1,4-divinylbenzene
EEDQ	2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Impact ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
GC	gas chromatography
h or hr	hour(s)
HATU	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography

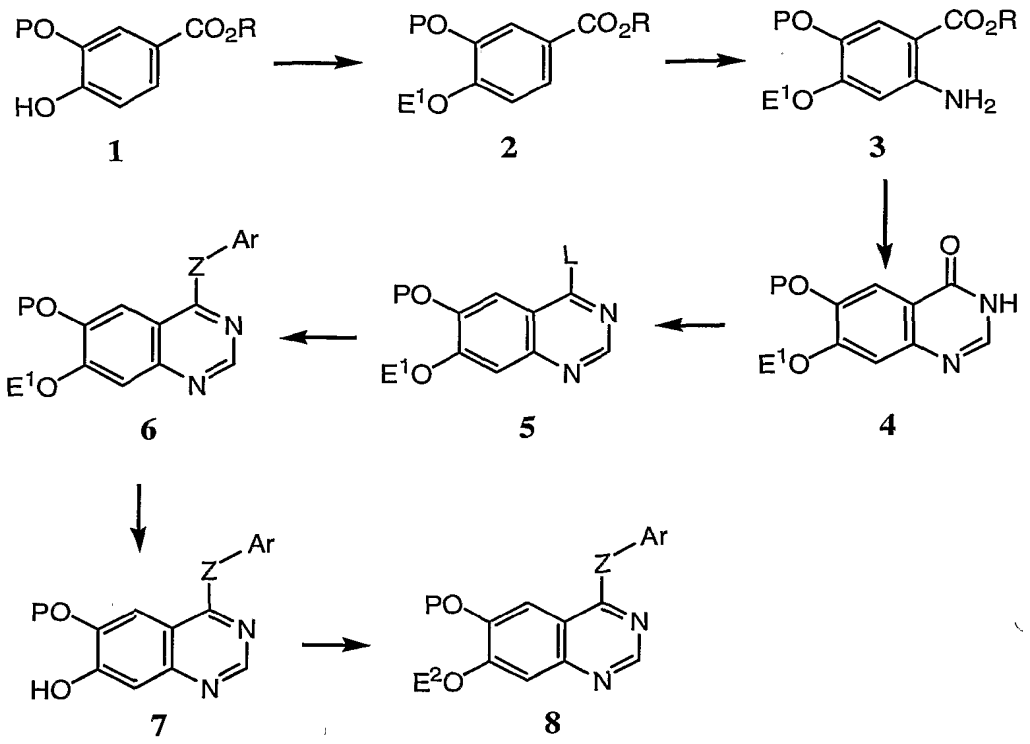
Abbreviation	Meaning
L	liter(s)
M	molar or molarity
m	multiplet
Me	methyl
mesyl	methanesulfonyl
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
nM	nanomolar
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	phenyl
PhOH	phenol
PfP	pentafluorophenol
PfPy	pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet

Abbreviation	Meaning
RT	Room temperature
Sat'd	saturated
s	singlet
s-	secondary
t-	tertiary
t or tr	triplet
TBDMS	t-butyldimethylsilyl
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
tosyl	p-toluenesulfonyl
Trt	triphenylmethyl
uL	microliter(s)
uM	Micromole(s) or micromolar

Synthesis of Compounds

[0279] Schemes 1 and 2 depict general synthetic routes for compounds of the invention and are not intended to be limiting. More specifically, Scheme 1 depicts synthesis of quinazoline compounds, and Scheme 2 depicts synthesis of quinoline compounds. Specific examples are described subsequently to these general synthetic descriptions so as to allow one skilled in the art to make and use either quinazolines or quinolines of the invention.

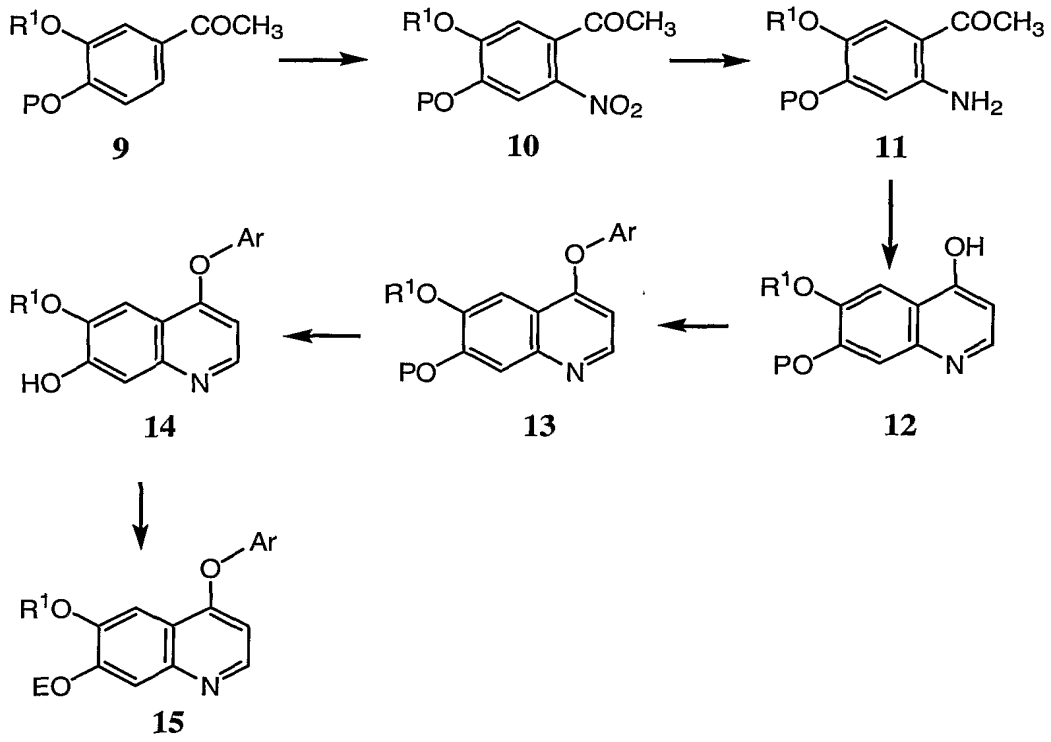
Scheme 1



[0280] Referring to Scheme 1, a benzoic ester **1**, where R is typically but not necessarily a methyl radical and P is typically but not necessarily an alkyl group, is O-alkylated at the oxygen *para* to the carboxylate group with an electrophile to afford a substituted derivative **2**. P is typically a lower alkyl group, but may be a protecting group that is removed later in a synthesis. When P is a lower alkyl group it may possess functionality initially, or be derivitized to contain such functionality at various stages of the synthesis. The group, E^1, may represent either a protecting group, e.g. benzyl, or a group that either has moieties present in compounds of the invention or possesses functionality that serve as a precursors to such groups. Aromatic ring nitration and reduction of the corresponding nitro group are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **3**. Formation of quinazolin-4-one **4** is carried out by methods well known in the art, for example by heating **3** in formamide solution in the presence of ammonium formate or for example by heating directly with formamidine hydrochloride. Introduction of 4-position functionality groups is carried out by methods known in the art. For example, quinazolin-4-one **4** is converted to an intermediate quinazoline **5**, where "L" represents a leaving group, e.g. chlorine. Quinazoline **5** is then converted to **6** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols. After formation of **6**, group "Z" is either left "as is" or converted at some subsequent stage to a derivative thereof. For example when Z is -NH-, then the hydrogen on the nitrogen

may optionally be replaced with an alkyl group, or when Z is sulfur, then that sulfur atom may be oxidized to, for example, a sulfone. Structure **6** may represent compounds of the invention or, for example when E^1 serves as a protecting group, E^1 may be removed to provide phenol **7**. Introduction of a group E^2 is carried out by methods well established in the art; for example alkylation with an appropriately derivatized alkyl halide (or mesylate or the like) to give **8** which also represents compounds of the invention.

Scheme 2



[0281] Scheme 2 shows a general route used to make exemplary quinolines of the invention. For example, compound **9** contains an alkyl group, R^1, a protecting group, P. The arrangement of the protected and alkylated phenolic oxygens may vary from the pattern depicted in compound **9**. Compound **9** is nitrated to provide compound **10**. The nitro group of compound **10** is reduced to give aniline **11**. Compound **11** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form 4-hydroxy quinoline **12**. Quinoline **12** may be converted to compounds of the invention in a number of ways. For example, the 4-oxygen is used as a nucleophile in a nucleophilic aromatic substitution reaction to form quinoline-aryl-ether **13**. In another example, compound **13** is further derivatized, via removal of protecting group P, to afford compound **14**. The 7-hydroxy of compound **14** is alkylated, for example with electrophile E, to provide a compound of the invention. As discussed in relation to Scheme 1,

variations on any of the above steps are possible, and intermediates in these schemes, for example compounds **12**, **13**, and **14** may also be compounds of the invention according to formula **I**. Also, for example, the 4-hydroxy quinoline compound **12** are converted to a corresponding 4-nitrogen or 4-sulfur quinoline using chemistry known in the art to make compounds of the invention, or alternatively the corresponding 4-nitrogen or 4-sulfur quinolines are made via routes analogous to that depicted in Schemes 1 and 2.

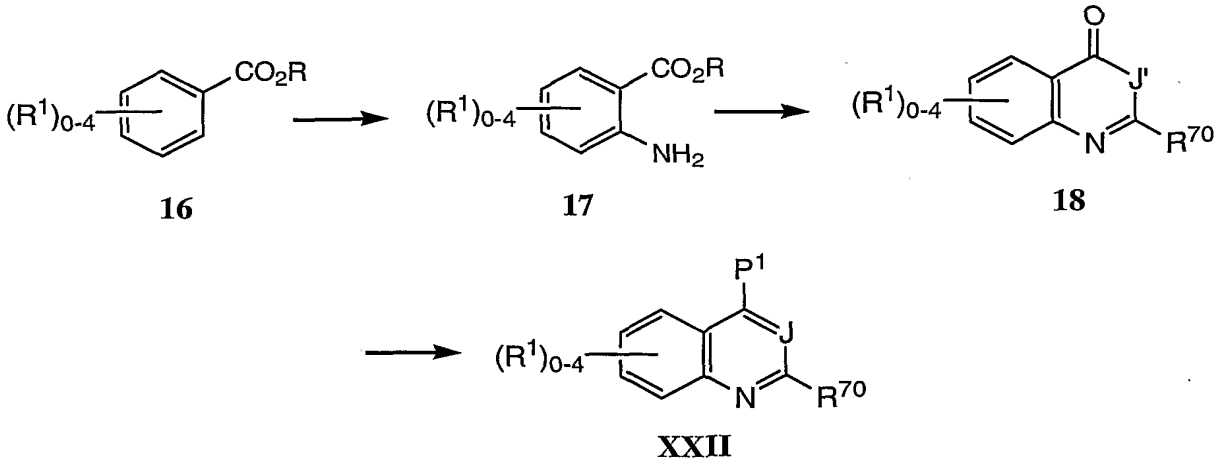
[0282] Schemes 1 and 2 are illustrative of quinolines and quinazolines having oxygen substitution at their respective 6- and 7-positions; the invention is not so limited, but rather is intended to encompass quinolines and quinazolines not necessarily having substitution, oxygen or otherwise, at their respective 6- or 7-positions.

[0283] Schemes 3 and 4 depict generalized synthetic routes to show the process of the invention to make compounds of formua **XXI** and is not intended to be limiting. More specifically, Schemes 3 and 4 depict convergent syntheses of quinoline and quinazoline compounds as described herein. Specific examples are described subsequently to this general synthetic description so as to allow one of ordinary skill in the art to practice the invention.

[0284] Referring to Scheme 3, a benzoic ester **16** for example, where R is typically but not necessarily a methyl radical and R^1 is typically but not necessarily one or more alkoxy or hydroxy groups. In a typical synthesis, at least one of R^1 within Scheme 3 is a hydroxyl which is converted (or protected)via one or more steps to a group important to the activity of the compounds as described as kinase modulators (in the case that -OH itself is desired in the final compound, then deprotection affords the -OH, *vide supra*). Preferably, but not necessarily, this group is complete once the synthesis of **XXII** is complete. By building desired complexity into **XXII** prior to combination with **XXIII**, convergent syntheses' advantages over serial syntheses are realized more fully. Regioselective aromatic ring nitration, and reduction of the corresponding nitro group, are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **17**. Formation of quinazoline or quinoline 4-one **18** is carried out by methods well known in the art. For example by heating **17** in formamide solution in the presence of ammonium formate, or by heating **17** with formamidine hydrochloride, the quinazoline-4-one analog is made. In another example **17** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form the 4-hydroxy quinoline analog (a tautomer of the 4-one). In this scheme J' represents either carbon or nitrogen atom with

the appropriate number of hydrogens to fill their respective normal valence bonding schemes; J' is a precursor to J. Radicals J and R^{70} are in accord with formula **XXI**. Introduction of 4-position functionality is carried out by methods known in the art. For example, 4-one **18** is converted to **XXII**, where "P^1" represents a suitable leaving group (in accord with formula **XXI**), e.g. chlorine (via dehydration/chlorination of **18** to give **XXII**). In another example, a 4-hydroxy analog is converted to a sulfonyl ester, e.g. the trifluoromethane sulfonate.

Scheme 3

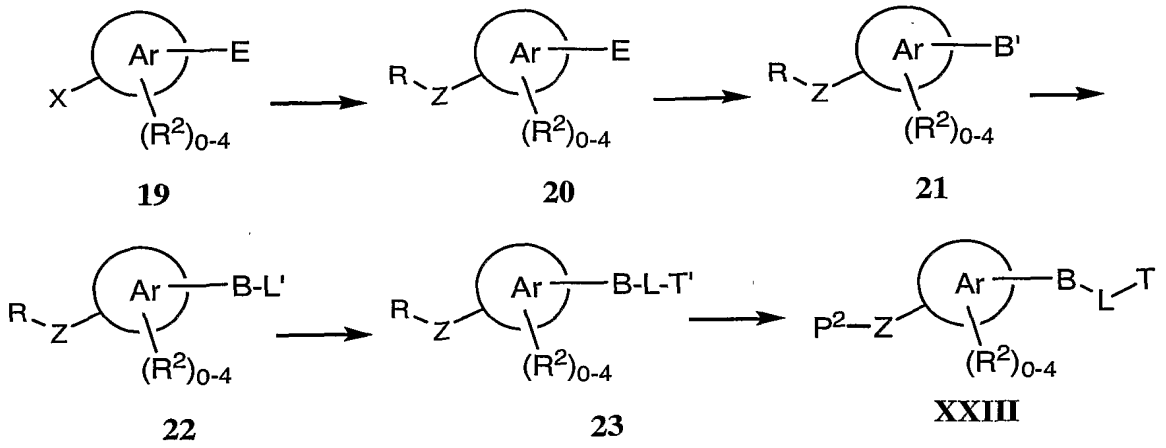


16 **17** **18**

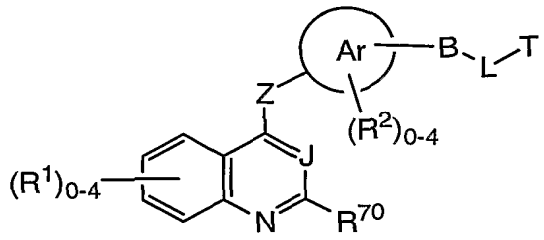
XXII

[0285] Scheme 4 shows a general route used to make compounds of formula **XXIII**. For example, aromatic compound **19**, where "X" is a leaving group, such as fluorine and "E" is an electron withdrawing group such as nitro, is converted to **20** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols (where "Z" is oxygen, nitrogen (substituted or not), or sulfur). In this case, "R" represents a removable group, for example benzyl. In a typical synthesis, after formation of **20**, group "E" is either left "as is" or converted at some subsequent stage to a derivative thereof. In the example depicted, E is converted to B', a precursor to B in accord with formula **XXI**, to make **21**. For example if E is a nitro, then B' could might be an amino group, made via reduction of the nitro group. Structure **21** may be further derivitized by synthesis of –B-L-T in accord with formula **XXI**. In scheme 4, this is depicted as a serial process whereby L', a precursor to L, is introduced to give **22**, followed by introduction of T' (a precursor to T) to give **23**. In some cases, -L-T is preformed and appended to B. One of ordinary skill in the art would appreciate that variations on any of the above steps are possible. Compound **23** is converted to **XXIII** via conversion of T' to T and introduction of P^2 (for example, when R is benzyl, removal of the benzyl after completion of –B-L-T).

Scheme 4



[0286] As discussed above, one aspect of the invention encompasses combination of **XXII** and **XXIII** to make compounds of formula **XXI**. Because of the diversity and complexity of compounds described for kinase modulation (*vide supra*), methods of the invention provide advantages to serial synthesis.



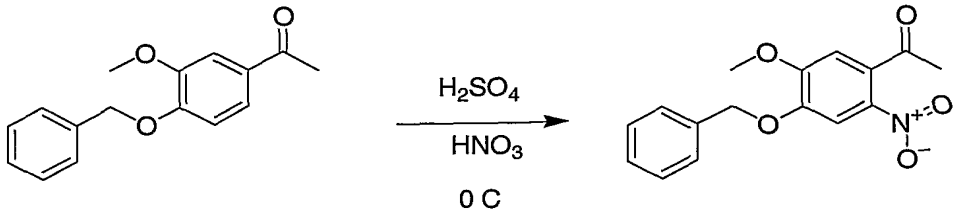
XXI

Examples

[0287] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, but not necessarily, each example set out below describes a multi-step synthesis as outlined above.

Quinoline and Quinazoline Syntheses

Example 1

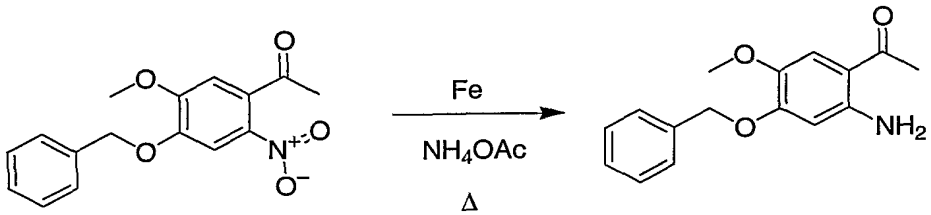


[0288] Synthesis of 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone. 1-(4-Benzyloxy-3-methoxy-phenyl)-ethanone (200 mmol, 51.3 g) dissolved in DCM (750ml) and the mixture cooled to 0° C. Nitric acid (90%, 300 mmol, 14 ml) was added dropwise to the cooled solution over 20 minutes. Sulfuric acid (96.2%, 300 mmol, 8.75 ml) was then added dropwise over 40 minutes at 0° C.

[0289] Additional nitric acid (200 mmol, 9.4 ml) was added dropwise over 20 minutes. The reaction mixture was diluted with water (300 ml) and wash with water (3 X 200 ml), Sat. NaHCO3 (4 X 200 ml, or until neutral). The organic layer was dried over Na2SO4 and concentrated.

[0290] The crude mixture was recrystallized with DMF to give 22.5 g of the nitro product. The DMF layer was concentrated and recrystallized with ethyl acetate to give additional 8.75g of the product. The ethyl acetate layer was concentrated and purified on silica column using 20% EtOAc/hexanes to gave another 4.75 g of the product. Total yield is 36 g, (~60%). 1H NMR (CDCl3): 7.647 (1H, s), 7.446-7.333 (5H, m), 6.745 (1H, s), 5.210 (2H, s), 3.968 (3H, s), 2.487 (3H, s).

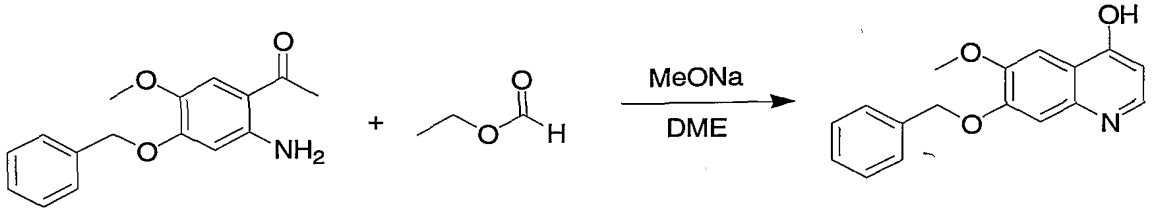
Example 2



[0291] Synthesis of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone. A Mixture of iron powder (477 mmol, 27 g), ammonium acetate (500 mmol, 31.g), 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone (120 mmol, 36 g), toluene (500 ml) and water (500 ml) was refluxed overnight, or until completion. The mixture was filtered through celite and

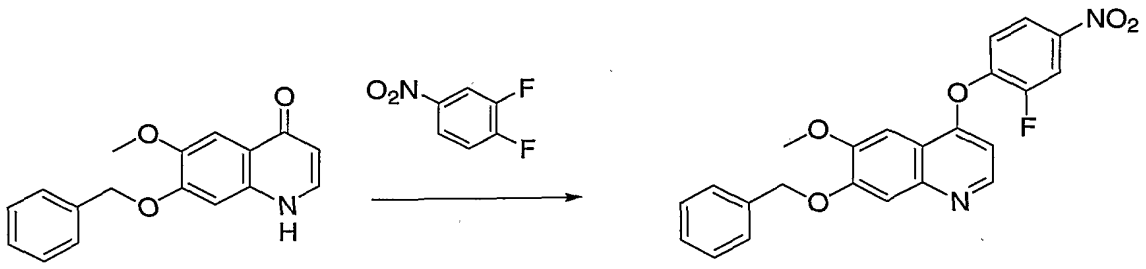
washed with EtOAc. The organic layer was washed with water and Sat. NaCl, dried over Na2SO4, and concentrated to afford the product, 90%. 1H NMR (CDCl3): 7.408-7.298 (5H, m), 7.130 (1H, s), 6.155 (2H, br), 6.104 (1H, s), 5.134 (2H, s), 3.834 (3H, s), 2.507 (3H, s). LC/MS (M+1 = 272).

Example 3



[0292] Synthesis of 7-Benzyloxy-6-methoxy-quinolin-4-ol. To a solution of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone (108 mmol, 29.3 g) in DME (700 ml) was added sodium methoxide (432 mmol, 23.35 g). The mixture was stirred for 30 minutes. Ethyl formate (540 mmol, 44 ml) was added and the mixture was stirred overnight. (Additional sodium methoxide may be needed if reaction is not complete as monitored by LC/MS.) After the reaction was completion, the mixture was diluted with water (40 ml) and acidified to neutral with 1M HCl. The precipitate was filtered and washed with water, dried *in vacuo* to afford 22g (72%) of 7-benzyloxy-6-methoxy-quinolin-4-ol. 1H NMR (CDCl3): 10.7 (1H, br), 7.703 (1H, s), 7.493-7.461 (1H, t), 7.431-7.413 (2H, br d), 7.372-7.333 (2H, t), 7.296-7.283 (1H, d), 6.839 (1H, s), 6.212-6.193 (1H, d), 5.212 (2H, s), 3.965 (3H, s). LC/MS (M+1 = 282).

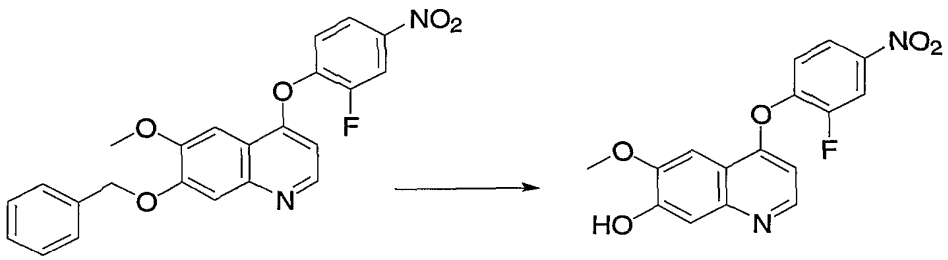
Example 4



[0293] 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 7-Benzyloxy-6-methoxy-1H-quinolin-4-one (12.2 g, 43.3 mmol, 1.0 eq.), acetonitrile (150ml), DMF (150ml) and

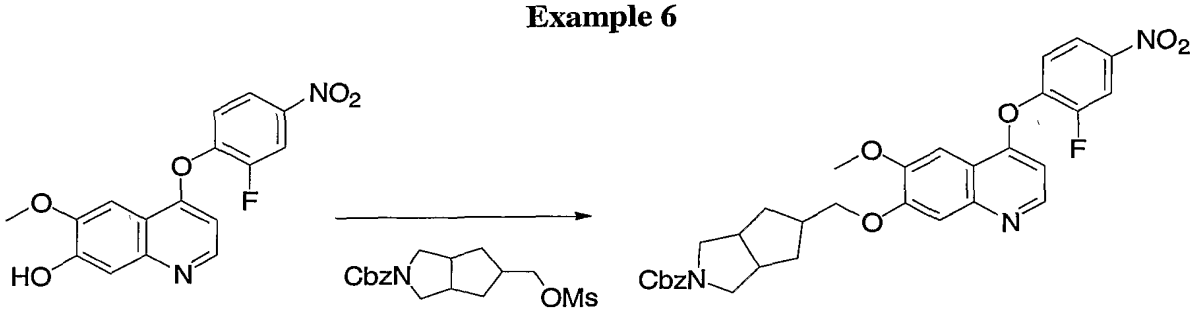
cesium carbonate (28.2 g, 86.5 mmol, 2.0 eq). The mixture was stirred at room temperature for 30 minutes at which time 1,2-difluoro-4-nitro-benzene (7.57 g, 47.6 mmol, 1.1 eq) was added over a 10 minute period. After 2 hours the reaction was complete at which time 75% of the MeCN and DMF was removed and the resulting solution was poured over into ice water. The solid was filtered and dried and further columned with a biotage system. The eluent was 1:3 ethyl acetate/hexane. Removal of the solvent afforded 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline as a pale green solid (7.4 g, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 8.42 (dd, 1H), 8.16 (m, 1H), 7.5 (m, 8H), 6.76 (d, 1H), 5.31 (s, 2H), 3.92 (s, 3H); MS (EI) for $C_{23}H_{27}FN_2O_5$: 421 (MH^+).

Example 5



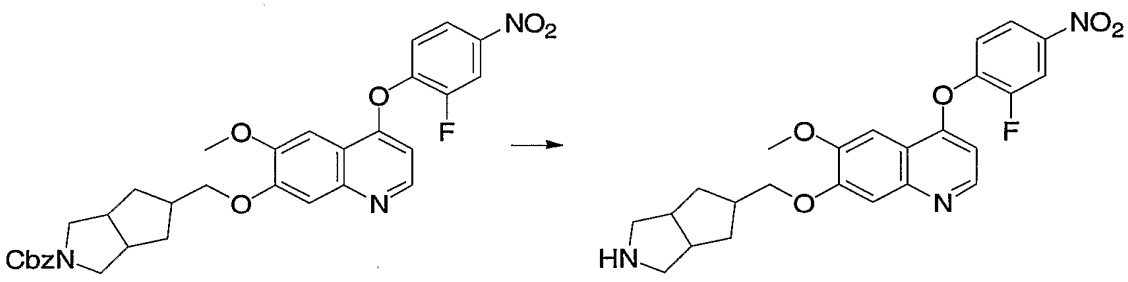
[0294] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol. To a round bottom flask equipped with a magnetic stir bar was added 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (2.9 g, 6.9 mmol, 1.0eq) and 33% HBr in acetic acid (30 ml). The mixture was stirred at room temperature for 3 hours and diluted with ether to give a pale white solid. The solid was filtered, washed with ether and dried to yield 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol as a pale white solid (2.74 g, 97.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 11.89 (bs, 1H), 8.87 (d, 1H), 8.57 (d, 1H), 8.30 (d, 1H), 7.89 (m, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 4.03 (s, 3H); MS (EI) for $C_{16}H_{11}FN_2O_5$: 421 ($M+H^+$).

Example 6



[0295] 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol (2.74 g, 6.7 mmol, 1.0 eq.), DMA (30ml) and cesium carbonate (6.6 g, 20.2 mmol, 3.0 eq). The mixture was stirred at room temperature for 30 minutes at which time 5-methanesulfonyloxymethyl-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (2.6 g, 7.3 mmol, 1.1 eq) was added. The reaction was heated to 75^0 C and allowed to stir overnight. After allowing the reaction to cool to room temperature the reaction was poured into water. The solid was filtered and was then dissolved in EtOAc and washed 2X water, 1X brine and dried over $NaSO_4$. The solvent was removed to yield 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester as a cream solid (3.7 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (d, 1H), 8.15 (d, 1H), 8.09 (d, 1H), 7.32 (m, 8H), 6.52 (d, 1H), 5.11 (d, 2H), 4.13 (d, 2H), 3.95 (s, 3H), 3.57 (m, 2H), 3.43 (m, 2H), 2.93 (m, 3H), 2.16 (m, 2H), 1.39 (m, 2H); MS (EI) for $C_{32}H_{30}FN_3O_7$: 588 ($M+H^+$).

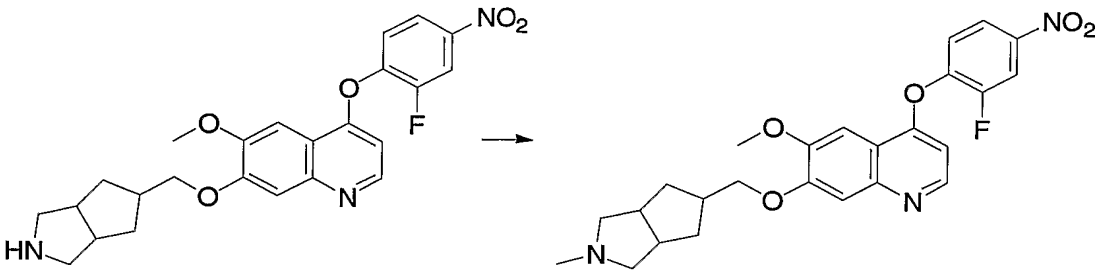
Example 7



[0296] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydrocyclopenta-[c]pyrrole-2-carboxylic acid benzyl ester (2.5 g, 4.1 mmol, 1.0eq), 33% HBr in acetic acid (5 ml) and acetic acid (5 ml). The mixture was stirred at room temperature for 1 hour and diluted with EtOAc to give a pale orange solid. The solid was filtered, washed with EtOAc and dried, giving 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.83 (d, 1H), 8.32 (m, 2H), 8.02 (s, 1H), 7.76 (t, 1H), 7.65 (s, 1H), 6.89 (d,

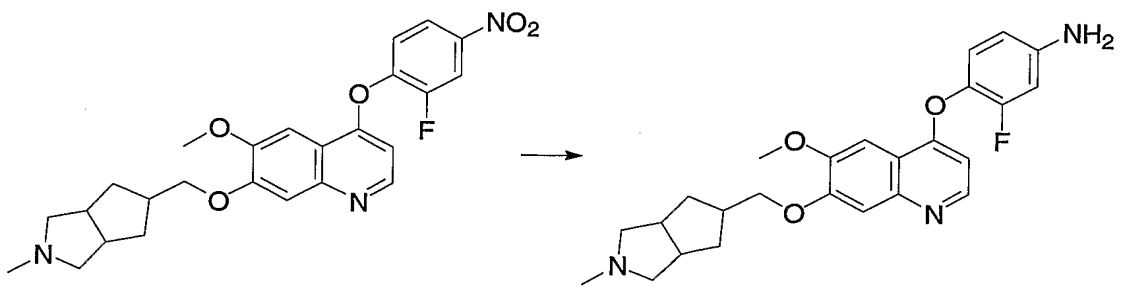
1H), 5.3 (d, 2H), 4.11 (m, 3H), 3.26 (m, 4H), 2.95 (m, 2H), 2.68 (m, 3H), 2.36 (m, 2H), 1.68 (m, 2H); MS (EI) for $C_{24}H_{24}FN_3O_5$: 454 ($M+H^+$).

Example 8



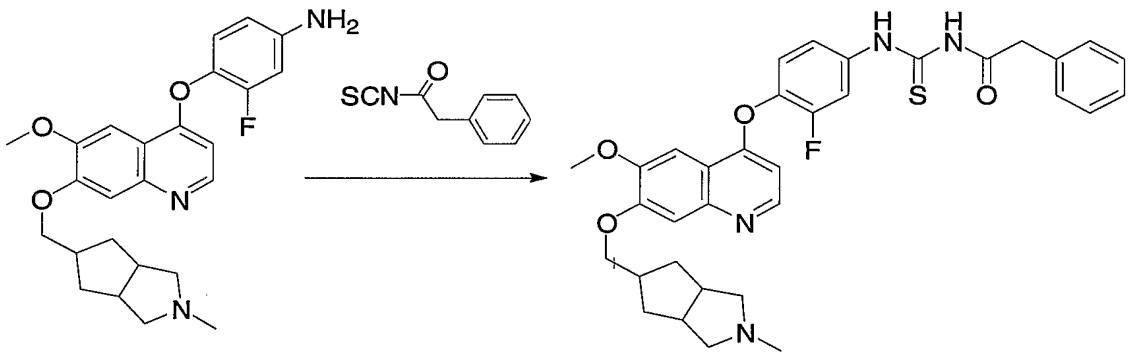
[0297] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 3.9 mmol, 1.0 eq.) and acetonitrile/water 1:1 (5ml, 5ml). The reaction mixture was then cooled to 0^0 C and 37% solution of formaldehyde in water was added (0.2 g, 7.8 mmol, 2.0 eq). While keeping the temperature at 0^0C $Na(OAc)_3BH$ was added (4.4g, 20.7 mmol, 3.0 eq). After 1 hour the pH was adjusted to 10 and the aqueous was extracted 2 x DCM (100 ml). Removal of the DCM resulted in a white solid. The compound was further purified with a biotage system using an eluent EtOAc and 5% MeOH, affording 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydrocyclopenta-[c]pyrrol-5-ylmethoxy)-quinoline (0.9 g, 50% yield).). ^{1}H NMR (400 MHz, $CDCl_3$): 8.57 (d, 1H), 8.14 (dd, 1H), 8.12 (dd, 1H), 7.41 (s, 2H), 7.34 (t, 1H), 6.54 (d, 1H), 4.19 (d, 2H), 4.01 (s, 3H), 2.61 (m, 4H), 2.43 (m, 1H), 2.33 (s, 3H), 2.11 (m, 4H), 1.32 (m, 2H); MS (EI) for $C_{25}H_{26}FN_3O_5$: 468 ($M+H^+$).

Example 9



[0298] 3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine. To a par hydrogenation reaction vessel was added 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (0.800 g, 1.6 mmol, 1.0 eq.), DMF (50 ml), EtoAc (50ml), MeOH (50ml), TEA (5ml) and 10% Pd/C (200 mg). The vessel was placed on the par hydrogenator at 35 psi overnight. The Pd was filtered and the solvent removed to give 3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine as an off yellow solid (0.78 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.45 (d, 1H), 7.57 (s, 1H), 7.36 (s, 1H), 7.05 (t, 1H), 6.54 (m, 2H), 6.39 (d, 1H), 4.16 (d, 2H), 4.01 (s, 3H), 3.81 (m, 3H), 2.61 (m, 3H), 2.41 (m, 1H), 2.29 (s, 3H), 2.23 (m, 2H), 1.32 (m, 2H); MS (EI) for $C_{25}H_{28}FN_3O_3$: 438 ($M+H^+$).

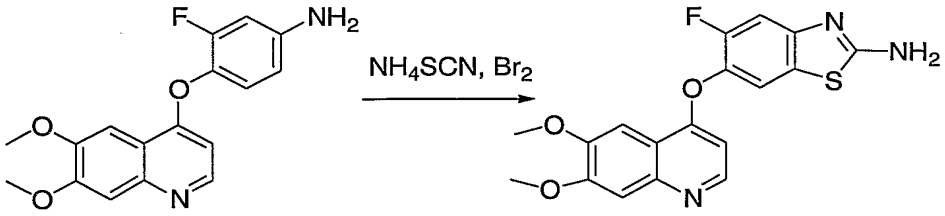
Example 10



[0299] 1-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea. To a round bottom flask equipped with a magnetic stir bar was added 3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine (0.78 mg, 1.7 mmol, 1.0 eq.), toluene (10ml), ethanol (10ml) and phenyl-acetyl isothiocyanate (1.64 g, 9.2 mmol, 4.5 eq). The reaction mixture was stirred at room temperature overnight. After removal of the solvent the product was purified with a biotage system using an eluent EtOAc and 4% TEA (2L) then EtOAc, 4% TEA, 1% MeOH (1L). The solvent was removed to give 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (0.5 g, 50% yield). ^{1}H NMR (400 MHz, DMSO): 8.48 (d, 1H), 7.92 (dd, 1H), 7.53 (s, 1H), 7.40 (m, 4H), 7.33 (d, 2H), 7.23 (m, 2H), 6.54 (d, 2H), 6.39 (d, 1H), 4.21 (d, 2H), 4.02 (s, 3H), 3.81 (m, 3H),

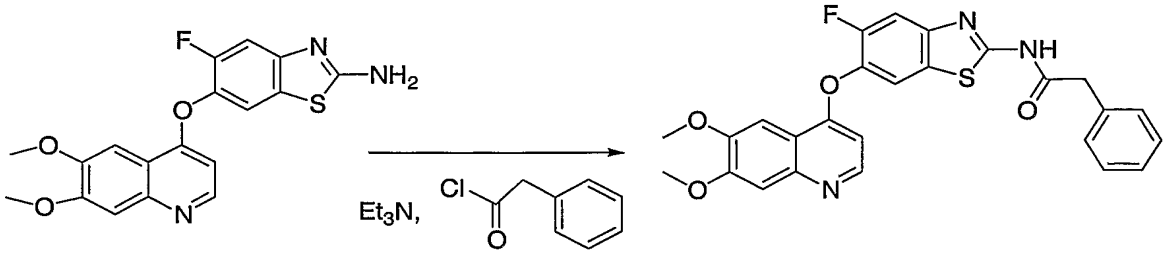
2.87 (d, 2H), 2.73 (m, 4H), 2.53 (m, 1H), 2.27 (m, 2H), 2.01 (s, 3H), 1.36 (m, 2H); MS (EI) for $C_{34}H_{35}FN_4O_4S$: 615 ($M+H^+$).

Example 11



[0300] 6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine. 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (1.00g, 3.18mmol) was dissolved in AcOH (8.0ml), to which was added NH_4SCN (486mg, 6.38mmol) and the mixture cooled in an ice bath. Br_2 (0.33ml, 6.42mmol) in AcOH (0.33ml) was added dropwise with stirring. After addition was complete, the reaction mixture was stirred at room temperature. After one hour, more NH_4SCN (1.0g, 13.1mmol) was added, followed by more Br_2 (0.33ml, 6.42mmol) in AcOH (0.33ml), dropwise with stirring. The reaction mixture was then heated to reflux for several minutes. Upon cooling to room temperature, solids were filtered and washed with AcOH, followed by H_2O. The volume of the filtrate was reduced *in vacuo* and the pH adjusted to pH 9-10 with 1.0N NaOH. The resulting solids were filtered, washed with H_2O, and dried under high vacuum to give 6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine (568mg, 48%). ^{1}H-NMR (400MHz, DMSO): 8.45 (d, 1H), 7.82 (d, 1H), 7.73 (br s, 2H), 7.53 (s, 1H), 7.38 (m, 2H), 6.44 (d, 1H), 3.94 (s, 6H). LC/MS Calcd for $[M+H]^+$ 372.1, found 372.2

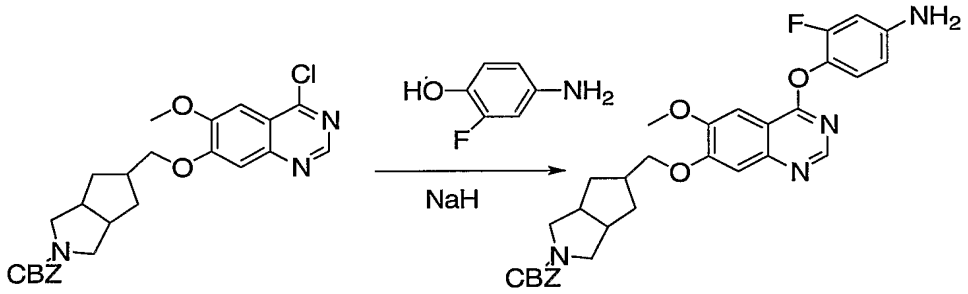
Example 12



[0301] N-[6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide. 6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine (95mg,

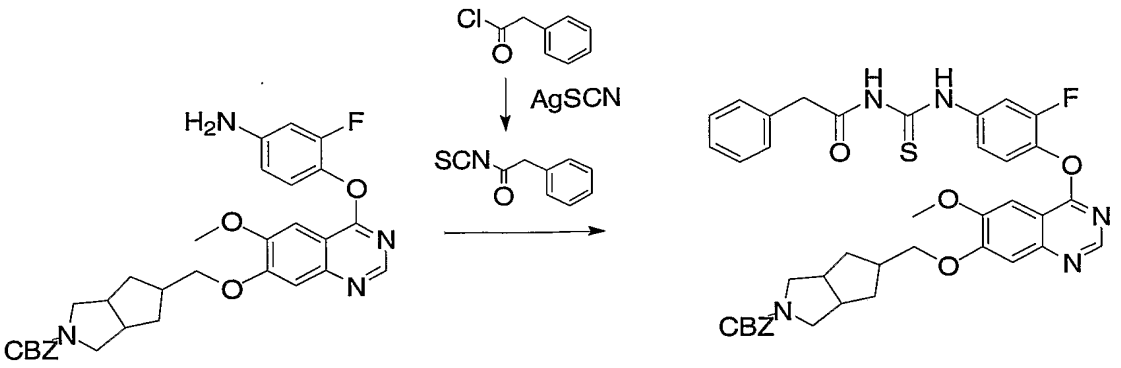
0.25mmol), Et_3N (0.10ml, 0.72mmol), phenylacetyl chloride (0.044ml, 0.33mmol), and THF (1.0ml) were combined and stirred at room temperature for 1 hr. Additional phenylacetyl chloride (0.044ml, 0.33mmol) was added and the mixture heated to reflux for 1-2 hrs. After cooling to room temperature, the reaction mixture was diluted with 1:1 AcCN:H_2O (1.0ml) and the resulting solids filtered, washed with 1:1 AcCN:H_2O and dried under high vacuum to give N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide (72mgs, 59%). ^{1}H-NMR (400MHz, DMSO): 12.80 (s, 1H), 8.54 (d, 1H), 8.18 (d, 1H), 7.91 (d, 1H), 7.60 (s, 1H), 7.45 (s, 1H), 7.34 (m, 4H), 7.28 (m, 1H), 6.60 (d, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.86 (s, 2H). LC/MS Calcd for $[M+H]^+$ 490.1, found 490.0.

Example 13



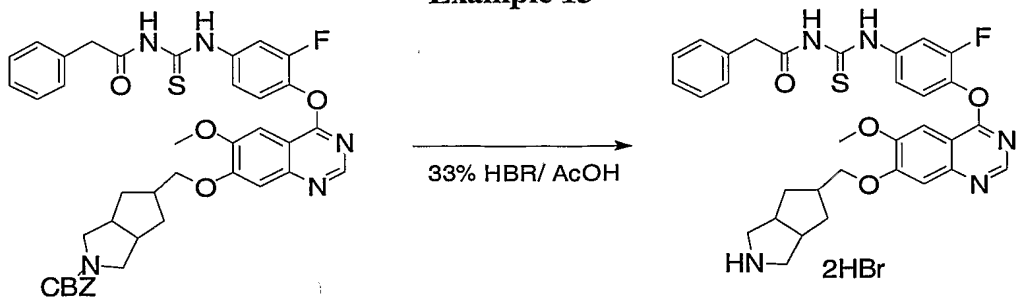
[0302] 5-[4-(4-Amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. 4-Amino-2-fluoro-phenol (1.53g, 12.0mmol) was dissolved in dry DMF (30ml) to which was added 60% NaH (774mg, 19.3mmol). After the mixture was stirred at room temperature for several minutes, a suspension of 5-(4-chloro-6-methoxy-quinazolin-7-yloxymethyl)-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (4.70g, 6.7mmol) in dry DMF (40ml) was added. The reaction mixture was stirred at room temperature for 1-2 hrs, then diluted with EtOAc and washed with sat'd $NaHCO_3$ (3x), H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo* to give crude 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, ~100%) which was used in the next reaction without further purification. ^{1}H-NMR (400MHz, DMSO): 8.50 (s, 1H), 7.48 (s, 1H), 7.34 (m, 5H), 7.28 (m, 1H), 7.02 (t, 1H), 6.48 (dd, 1H), 6.40 (dd, 1H), 5.40 (br s, 2H), 5.05 (s, 2H), 4.16 (d, 2H), 3.92 (s, 3H), 3.48 (m, 2H), 3.30 (m, 2H), 2.65 (m, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 559.2, found 559.4.

Example 14



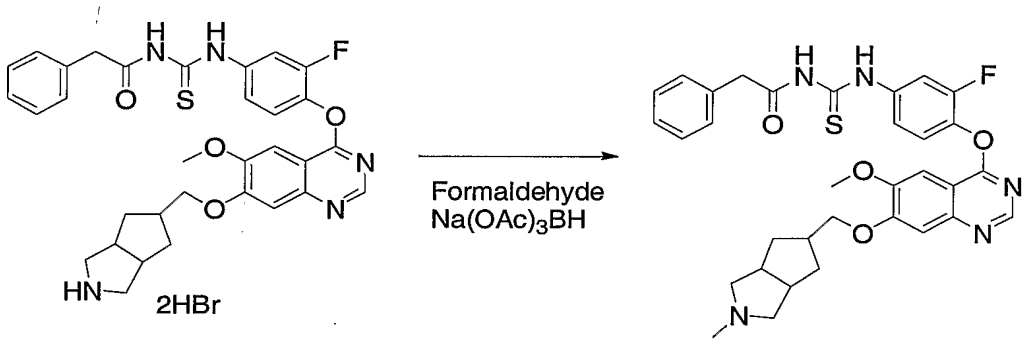
[0303] 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. Phenylacetyl chloride (2.65ml, 20.0mmol) and AgSCN (4.92g, 29.6mmol) were combined in dry toluene (50ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated *in vacuo*. The resulting oil was combined with 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, 10mmol) in 1:1 EtOH:toluene (100ml) and the mixture stirred at room temperature for 1-2 hrs. The reaction mixture was diluted with EtOAc and washed with sat'd $NaHCO_3$ (3x), H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (3:1 EtOAc:hexanes) to give 5-{4-[2-fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydrocyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (3.61g, 49%) as a dark brown foam. ^{1}H-NMR (400MHz, DMSO): 12.44 (s, 1H), 11.80 (s, 1H), 8.54 (s, 1H), 7.90 (m, 1H), 7.53 (s, 1H), 7.48 (m, 2H), 7.38 (s, 1H), 7.34 (m, 7H), 7.28 (m, 3H), 5.05 (s, 2H), 4.16 (d, 2H), 3.94 (s, 3H), 3.72 (s, 2H), 3.48 (m, 2H), 3.30 (m, 2H), 2.65 (m, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 736.2, found 736.0.

Example 15



[0304] 1-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt. 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (3.3g, 4.5mmol) was dissolved in AcOH (70ml) to which was added 33%HBr in AcOH (12ml). The reaction mixture was stirred at room temperature for 1 hr, diluted with Et_2O (1000ml) and the resulting solids filtered, washed with Et_2O, and dried under high vacuum to give the 1-{3-fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt (3.4g, 100%). ^{1}H-NMR (400MHz, DMSO): 12.42 (s, 1H), 11.80 (s, 1H), 8.84 (br s, 2H), 8.64 (s, 1H), 7.92 (m, 1H), 7.59 (s, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.33 (m, 4H), 7.27 (m, 1H), 4.17 (d, 2H), 3.95 (s, 3H), 3.73 (s, 2H), 3.17 (m, 2H), 3.10 (m, 2H), 2.83 (m, 2H), 2.45 (m, 1H), 2.15 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 602.2, found 602.1.

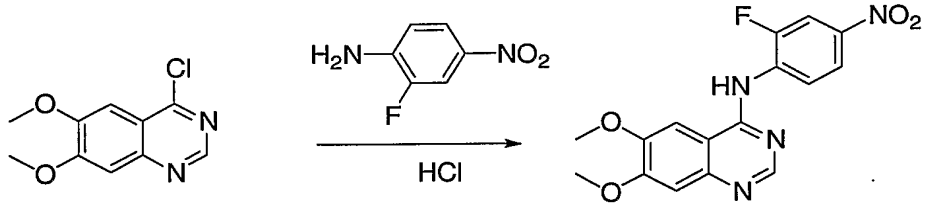
Example 16



[0305] 1-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea. 1-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt (3.4g, 4.5mmol) was dissolved in in a combination of AcCN (100ml), H_2O (30ml), and AcOH (2.45ml). Formaldehyde (37% in H_2O, 855ml, 10.5mmol) was added and the mixture cooled in an ice bath. $Na(OAC)_3BH$ (2.99g, 14.1mmol) was added and the reaction mixture was stirred at 0 C for 1 hr, followed by stirring at room temperature for 2 hrs. The reaction mixture was neutralized with the addition of sat'd $NaHCO_3$ and then concentrated *in vacuo*. The resulting aqueous mixture was extracted with CH_2Cl_2 (3x). The combined extractions were washed with sat'd $NaHCO_3$ (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The

resulting residue was purified by flash chromatography (100% EtOAc, followed by 4% Et_3N in EtOAc) to give the free base of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (1.13g, 40%). The free base was converted to the HCl salt by dissolving the free base in a mixture of 1:1 AcCN:H_2O containing 2-3 equivalents of 1 N HCl and lyophilizing to give the HCl salt of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea as a white solid. ^{1}H-NMR (400MHz, DMSO): 12.44 (s, 1H), 11.83 (s, 1H), 10.24 (br s, 1H), 8.59 (s, 1H), 7.93 (m, 1H), 7.59 (s, 1H), 7.50 (m, 2H), 7.42 (s, 1H), 7.36 (m, 4H), 7.30 (m, 1H), 4.20 (m, 2H), 3.95 (s, 3H), 3.73 (s, 2H), 3.39 (m, 2H), 3.06 (m, 2H), 2.95-2.77 (m, 5H), 2.35 (m, 1H), 2.15 (m, 2H), 1.45 (m, 2H). LC/MS Calcd for $[M+H]^+$ 616.2, found 616.2. Alternatively, the free base was converted to the acetate salt by dissolving the free base in a mixture of MeOH and CH_2Cl_2 to which was added 3 equivalents of acetic acid. The resulting mixture was concentrated *in vacuo* and the resulting residue lyophilized from 1:1 AcCN:H_2O to give the acetate salt of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea as a white solid. ^{1}H-NMR (400MHz, $CDCl_3$): d 12.45 (s, 1H), 8.65 (s, 1H), 7.98 (dd, 1H), 7.50 (s, 1H), 7.40 (m, 4H), 7.29 (m, 4H), 4.17 (d, 2H), 4.05 (s, 3H), 3.75 (s, 2H), 2.93 (m, 2H), 2.80 (m, 2H), 2.72 (m, 2H), 2.53 (s, 3H), 2.47 (m, 1H), 2.25 (m, 2H), 2.02 (s, 3H), 1.35 (m, 2H). LC/MS Calcd for $[M+H]^+$ 616.2, found 616.2.

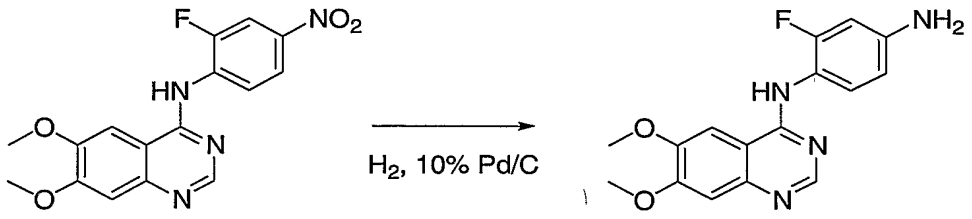
Example 17



[0306] (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine. A mixture of 4-chloro-6,7-dimethoxy-quinazoline (548mg, 2.4mmol), 2-fluoro-4-nitro-phenylamine (392mg, 2.5mmol), AcCN (10ml), and conc'd HCl (0.050ml) was heated to reflux for several hrs. After the reaction mixture was allowed to cool to room temperature, the resulting solids were filtered, washed with AcCN and air-dried to give (6,7-dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mgs, 80%). ^{1}H-NMR (400MHz,

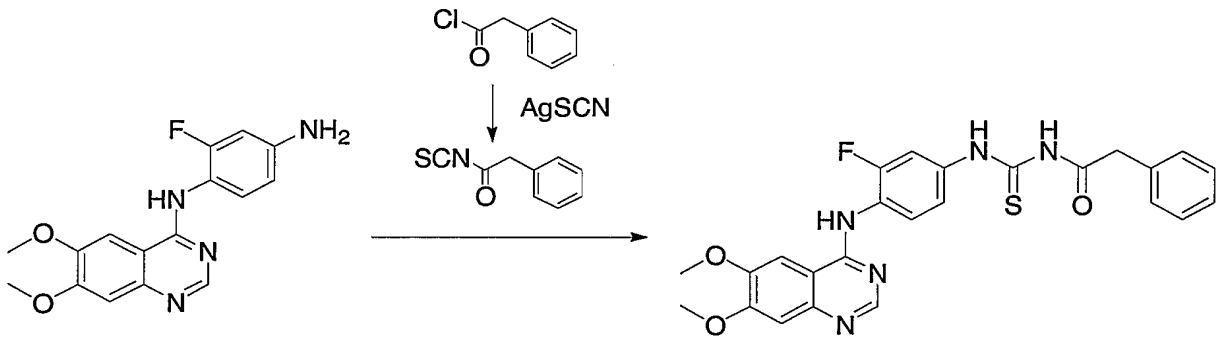
DMSO): 12.18 (br s, 1H), 8.91 (s, 1H), 8.45 (s, 1H), 8.36 (dd, 1H), 8.24 (dd, 1H), 7.91 (dd, 1H), 7.44 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H). LC/MS Calcd for $[M+H]^+$ 345.1, found 345.4.

Example 18



[0307] N[1]-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine. (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mg, 1.95mmol) was dissolved in a combination of DMF (20ml) and MeOH (20ml), to which was added 10% Pd/C (227mg). The mixture was shaken under an atmosphere of H_2 on a Parr hydrogenator at 40psi for 3hrs. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. The resulting residue was triturated in EtOAc/Et_2O. The resulting solids were filtered, washed with Et_2O, and dried under vacuum to give N[1]-(6,7-dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine (398mg, 65%) which was used in the next reaction without further purification. ^{1}H-NMR (400MHz, DMSO): 10.80 (br s, 1H), 10.30 (br s, 1H), 8.63 (s, 1H), 8.15 (s, 1H), 7.33 (s, 1H), 7.15 (m, 1H), 6.45 (m, 1H), 3.96 (s, 6H). LC/MS Calcd for $[M+H]^+$ 315.1, found 315.4.

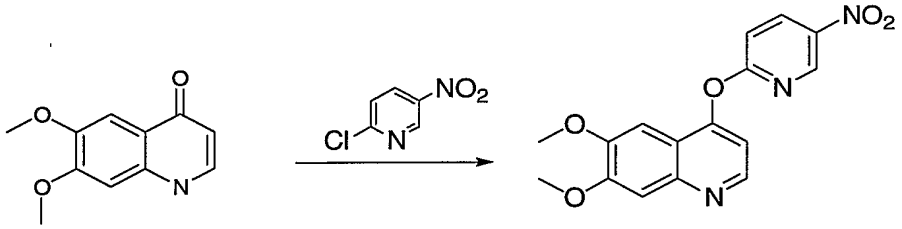
Example 19



[0308] 1-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)-3-fluoro-phenyl]-3-phenylacetyl-thiourea. Phenylacetyl chloride (0.18ml, 1.4mmol) and AgSCN (338mg, 2.0mmol) were

combined in dry toluene (5ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated *in vacuo*. The resulting oil was combined with N^1-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine (398mg, 1.3mmol) in 1:1:2 EtOH:toluene:MeOH (30ml) and the mixture stirred at room temperature overnight. The resulting solids were filtered and washed with toluene, followed by hexanes. The solids were dissolved/suspended in a mixture of EtOAc/MeOH. Insoluble material was filtered and the filtrate concentrated *in vacuo*. The resulting solids were once again dissolved/suspended in a mixture of EtOAc/MeOH. In soluble material was filtered and the filtrate concentrated *in vacuo* to give 1-[4-(6,7-dimethoxy-quinazolin-4-ylamino)-3-fluoro-phenyl]-3-phenylacetyl-thiourea (105mg, 17%). ^{1}H-NMR (400MHz, DMSO): 12.53 (s, 1H), 11.86 (s, 1H), 11.44 (br s, 1H), 8.81(s, 1H), 8.25 (s, 1H), 7.94 (dd, 1H), 7.54 (m, 2H), 7.16 (m, 5H), 7.10 (m, 1H), 4.02 (s, 6H), 3.84 (s, 2H). LC/MS Calcd for $[M+H]^+$ 492.1, found 492.4.

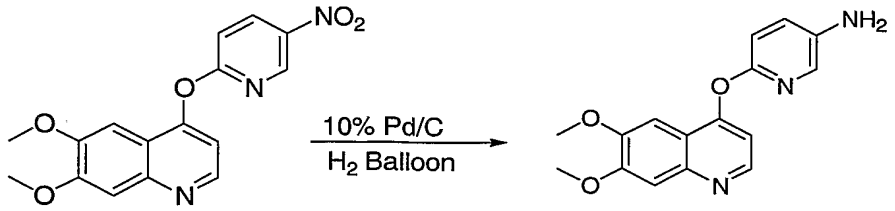
Example 20



[0309] 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-1*H*-quinolin-4-one (1.8 g, 8.77 mmol, 1.0 eq.), anhydrous acetonitrile (90 mL) and Cs_2CO_3 (3.13 g, 9.65 mmole, 1.1 eq.). The reaction mixture was stirred at room temperature for 5 minutes. Then, 2-Cl-5-nitropyridine (1.53 g, 9.65 mmol, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 16 hours. The solids were then filtered off and the filtrate was concentrated via rotary evaporation. The resulting material was taken up in EtOAc, and again the solids were filtered off. The EtOAc filtrate was concentrated. Purification was done on Biotage with solvent system EtOAc 100%. The collected pure fractions were concentrated and dried on high vacuum overnight to give 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline as a yellow foam solid (0.902 g, 31.4% yield). ^{1}H NMR (400

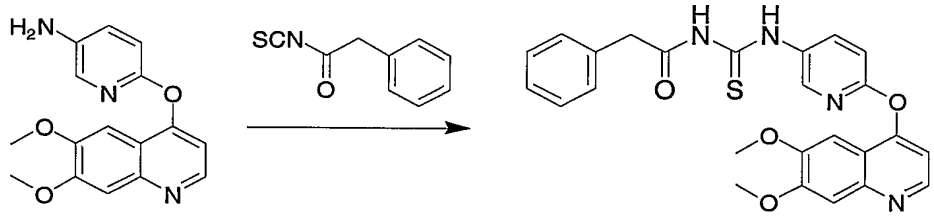
MHz, CDCl3): 9.08 (d, 1H), 8.74 (d, 1H), 8.60 (dd, 1H), 7.49 (s, 1H), 7.26 (d, 1H), 7.16 (s, 1H), 7.07 (d, 1H), 4.06 (s, 3H), 3.95 (s, 3H); MS (EI) for $C_{16}H_{13}N_3O_5$: 328 ($M+H^+$).

Example 21



[0310] 6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline (0.46 g, 1.41 mmol, 1.0 eq.), and THF (10 mL), MeOH (4 mL), DMF (2 mL), and TEA (2 mL). The 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline was dissolved completely in the above solution mixture, and was flushed with nitrogen for at least 5 minutes. The Pd/C (10% by weight) (0.090 g, 20% by weight) was then added. A balloon filled with H_2 was connected to the flask after the nitrogen was vacuumed out. The reaction mixture was stirred at room temperature for 4 hours. The palladium was filtered out through Celite, and the filtrated was collected and concentrated via rotary evaporation. The resulting oil-like product was taken up into 5 mL of water and 1 mL of acetonitrile and lyophilized to yield 6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine as a light brown solid (0.411 g, 98.1%). ^{1}H NMR (400 MHz, CDCl3): 8.54 (d, 1H), 7.85 (d, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 7.18 (dd, 1H), 6.96 (d, 1H), 6.61 (d, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.73 (s, 2H); MS (EI) for $C_{16}H_{15}N_3O_3$: 298 ($M+H^+$).

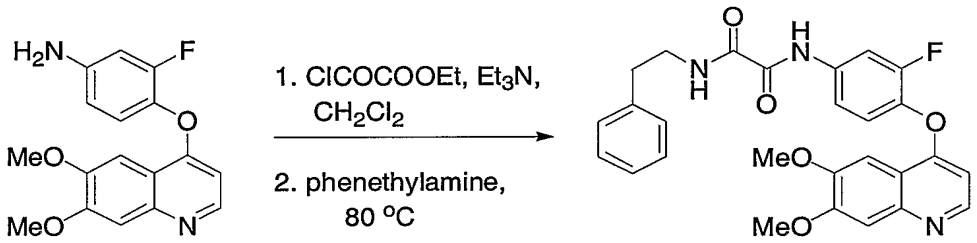
Example 22



[0311] 1-[6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-3-phenylacetyl-thiourea. To a round bottom flask equipped with a magnetic stir bar was added 6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine (85 mg, 0.0285 mmol, 1.0 eq.), and Phenyl-acetyl

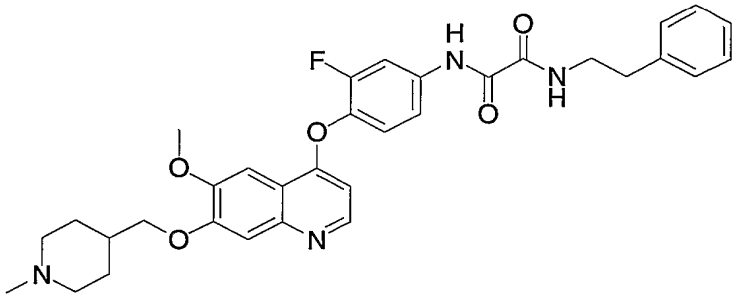
isothiocyanate (256 mg, 1.44 mmol, 5.0 eq.) dissolved in EtOAc/MeOH 50:50 (2 mL). The reaction mixture was sittred at room temperature for 12 hours, and the solvent was evaporated via rotary evaporation. Purification was done on Biotage with solvent system 95% EtOAc, 4% TEA and 1% MeOH. The combined pure fractions were concentrated and dried under vacuum overnight to yield 1-[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-3-phenylacetyl-thiourea as a light yellow solid (40.4 mg, 29.7%). ^{1}H NMR (400 MHz, CDCl3): 8.65 (d, 1H), 8.33 (d, 1H), 8.27 (dd, 1H), 7.35 (m, 7H), 7.15 (d, 1H), 6.92 (d, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.76 (s, 2H); MS (EI) for $C_{25}H_{22}N_4O_4S$: 475 ($M+H^+$).

Example 23



[0312] N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-phenethyl-oxalamide. To a solution of 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (263 mg, 0.83 mmol) and Et_3N (0.223 ml, 1.67 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of ethyl oxalyl chloride in CH_2Cl_2 (1 mL). The stirring was continued for 0.5 h at rt. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ and dried over $NaSO_4$. Removal of the solvent gave the crude oxamate, which was treated with neat phenethylamine (1.0 g, 8.3 mmol) at 80 °C for 3 h. Purification by flash column chromatography (hexanes:EtOAc = 1:3) gave N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-phenethyl-oxalamide (310 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (br s, 1 H), 8.70 (d, J = 6.3 Hz, 1 H), 7.83 (dd, J = 11.9, 2.5 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.43 (s, 1 H), 7.38-7.32 (m, 3 H), 7.30-7.20 (m, 4 H), 6.41 (d, J = 5.3 Hz, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 3.67 (dt, J = 7.0, 7.0 Hz, 2 H), 2.92 (t, J = 7.2 Hz, 2 H). LC-MS: 490 $[M+H]^+$

Example 24



[0313] N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxyl-phenyl}-N'-phenethyl-oxalamide. To a flask containing 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (850 mg, 2.0 mmol) was added 20 mL of 30% HBr in AcOH. The resulted solution was stirred for 4 h at rt; at this time, a large amount of precipitate formed. The crude product was filtered, washed with Et_2O and dried in air, giving 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 92% yield).

[0314] To a solution of the 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 1.8 mmol) in DMF (9 mL) was added K_2CO_3 (1.24 g, 9.0 mmol) and N-Boc-4-piperidinemethanol mesylate (732 mg, 2.5 mmol). The mixture was then stirred at 80 °C for 2.5 h. After it was cooled to rt, the mixture was loaded directly to a Biotage column, and eluted with solvents (hexanes:EtOAc = 1:3). The resulting product, 4-[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester, was obtained as a solid (556 mg, 56%).

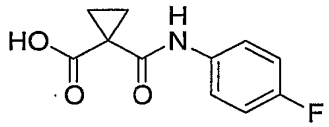
[0315] To a solution of 4-[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (305 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) was added 0.4 mL of TFA. The reaction mixture was stirred for 1.5 h and the solvents were removed under reduced pressure. The crude product was treated with $NaBH(OAc)_3$ (381 mg, 1.80 mmol) and formaldehyde (0.5 mL, 37% in H_2O). The stirring was continued for 12 h. The reaction was quenched with sat. aqueous $NaHCO_3$. 15% NaOH was added until PH = 14. The product was extracted with EtOAc. Removal of the solvent *in vacuo* gave the crude product, 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinoline, (240 mg, 93%), which was used directly in the next reaction.

[0316] To a solution of 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinoline (240 mg, 0.54 mmol) in EtOH (20 mL) was added 10% Pd/C (50

mg). The mixture was then hydrogenated on a Parr hydrogenator (40 psi) for 10 h. AcOH was added to dissolve the intermediate (mostly the hydroxylamine) and the hydrogenation was continued for additional 12 h. LC-MS was used to monitor the reaction progress. The solvents were removed under reduced pressure and the resulting crude product of 3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenylamine (about 220 mg) was used directly in the next reaction.

[0317] To a 0 °C solution of 3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenylamine (66 mg, 0.13 mmol) and Et_3N (0.34 mL) in CH_2Cl_2 (6 mL) was added slowly ethyl oxalyl chloride (98 mg). The reaction mixture was stirred at rt for 30 min, then diluted with CH_2Cl_2 and washed with sat. aqueous $NaHCO_3$. After dried over $MgSO_4$ and concentrated, the crude ethyl oxamate was reacted with phenethylamine (80 mg, 0.64 mmol) at 80 °C for 2 h. Purification by HPLC gave product, N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide (52 mg, 68% yield). ^1H NMR (400 MHz) δ 9.38 (br s, 1 H), 8.48 (d, J = 5.2 Hz, 1 H), 7.83 (dd, J = 11.7, 2.6 Hz, 1 H), 7.59 (t, J = 6.2 Hz, 1 H), 7.55 (s, 1 H), 7.40-7.20 (8 H), 6.39 (d, J = 5.3 Hz, 1 H), 4.06 (d, J = 6.6 Hz, 2 H), 4.04 (s, 3 H), 3.67 (q, J = 6.8 Hz, 2 H), 2.98 (br d, J = 11.5 Hz, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 2.34 (s, 3 H), 2.10-1.80 (m, 5 H), 1.60-1.54 (m, 2 H).

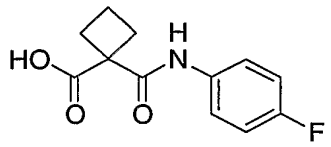
Example 25



[0318] 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, 1996, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (21.2 g, 0.163 mol, 1.0 eq.) in anhydrous THF (200 mL) under nitrogen was added dropwise triethylamine (16.49 g, 0.163 mol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (19.39 g, 0.163 mol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (19.92 g, 0.179 mol, 1.1 eq.) in anhydrous THF (100 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and

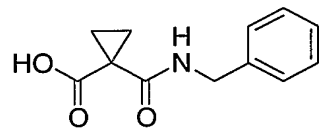
washed with 1N NaOH. The layers were separated, and the ethyl acetate layer was concentrated in vacuo to give a brownish solid. The brownish solid was washed with small amount of cold ethyl acetate, filtered and dried under vacuum to yield 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid as a white solid (23.71 g, 65.18%). ^{1}H NMR (400 MHz, CD_3OD): 7.57-7.53 (m, 2H), 7.05-7.00 (m, 2H) 1.46-1.43 (m, 2H), 1.40-1.37 (m, 2H).

Example 26



[0319] 1-(4-Fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid. To a mixture of cyclobutane-1,1-dicarboxylic acid (10.0 g, 69.4 mmol, 1.0 eq.) in anhydrous THF (100 mL) under nitrogen was added dropwise triethylamine (7.02 g, 69.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (8.25 g, 69.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (8.48 g, 76.3 mmol, 1.1 eq.) in anhydrous THF (50 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH. The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-(4-fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid as a light pink solid (5.75 g, 34.9%). ^{1}H NMR (400 MHz, $CDCl_3$ w/1drop CD_3OD): 7.53-7.48 (m, 2H), 7.06-7.00 (m, 2H), 2.81-2.63 (m, 4H), 2.14-2.02 (m, 2H).

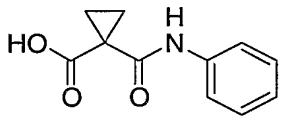
Example 27



[0320] 1-Benzylcarbamoyl-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, 1996, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (5.0 g, 38.4

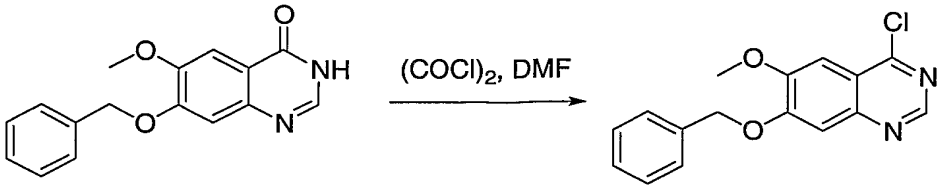
mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (3.89 g, 38.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.57 g, 38.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of benzylamine **5** (4.53 g, 42.3 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH 10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-Benzylcarbamoyl-cyclopropanecarboxylic acid as a white solid (4.39 g, 52.15%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.44 (br s, 1H), 7.37-7.33 (m, 2H), 7.32-7.26 (m, 3H), 1.82-1.70 (m, 4H).

Example 28



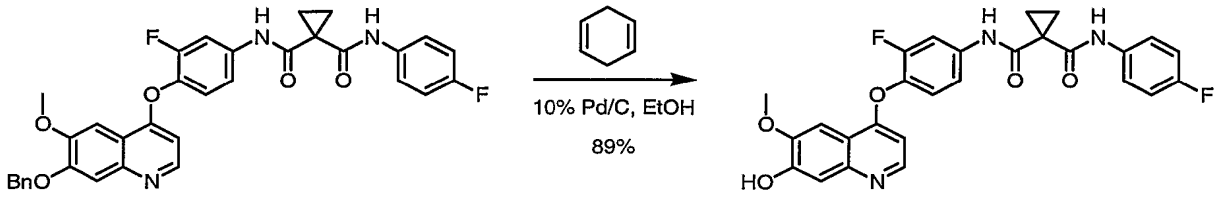
[0321] 1-Phenylcarbamoyl-cyclopropanecarboxylic acid. To a mixture of cyclopropane-1,1-dicarboxylic acid (5.29 g, 40.7 mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (4.12 g, 40.7 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.84 g, 40.7 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of phenylamine 9 (4.17 g, 44.8 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH >10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-phenylcarbamoyl-cyclopropanecarboxylic acid as a white solid (5.08 g, 60.8%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (br s, 1H), 7.56-7.54 (m, 2H), 7.35-7.31 (m, 2H), 7.15-7.10 (m, 1H), 1.94-1.91 (m, 2H), 1.82-1.79 (m, 2H).

Example 29



[0322] 7-Benzyloxy-4-chloro-6-methoxy-quinoline. Dry DMF (8.0ml, 103mmol) was dissolved in dry $CHCl_3$ (40ml) and cooled in an ice bath. Oxalyl chloride (9.0ml, 105mmol) in CH_2Cl_2 (10ml) was added dropwise with stirring at 0C. When the bubbling had ceased, this solution was added slowly to an ice-cold solution of 7-benzyloxy-6-methoxy-3H-quinazolin-4-one (10.0g, 35.4mmol) in dry $CHCl_3$ (60ml) and the mixture was then heated to reflux for 2-3hrs. After cooling to room temperature, H_2O (100ml) was added and the phases were separated. The aqueous phase was further extracted with $CHCl_3$ (2x). The combined $CHCl_3$ extractions were washed with sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 100%EtOAc) to give 7-benzyloxy-4-chloro-6-methoxy-quinoline (5.11g, 48%). LC/MS Calcd for $[M+H]^+$ 301.1, found 301.1.

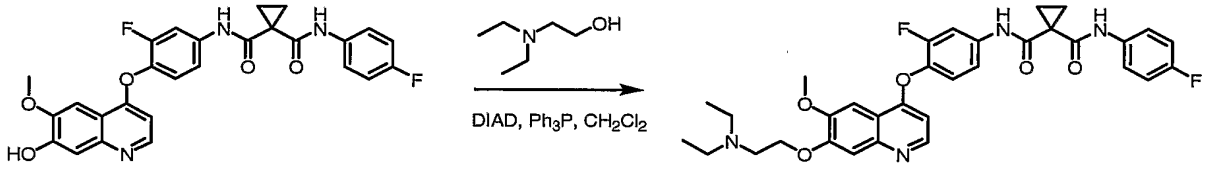
Example 30



[0323] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide. To a solution of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (1.18g, 2.0 mmol) in EtOH (20 mL) was added 1,4-cyclohexadiene (2.0 mL, 20 mmol) and 10% Pd/C (300 mg). The reaction mixture was then heated to reflux and the stirring was continued for 2 h. It was cooled to room temperature, filtered through celite and washed with MeOH. The MeOH solution was then concentrated under reduced pressure. The residue was taken into EtOAc (200 mL).

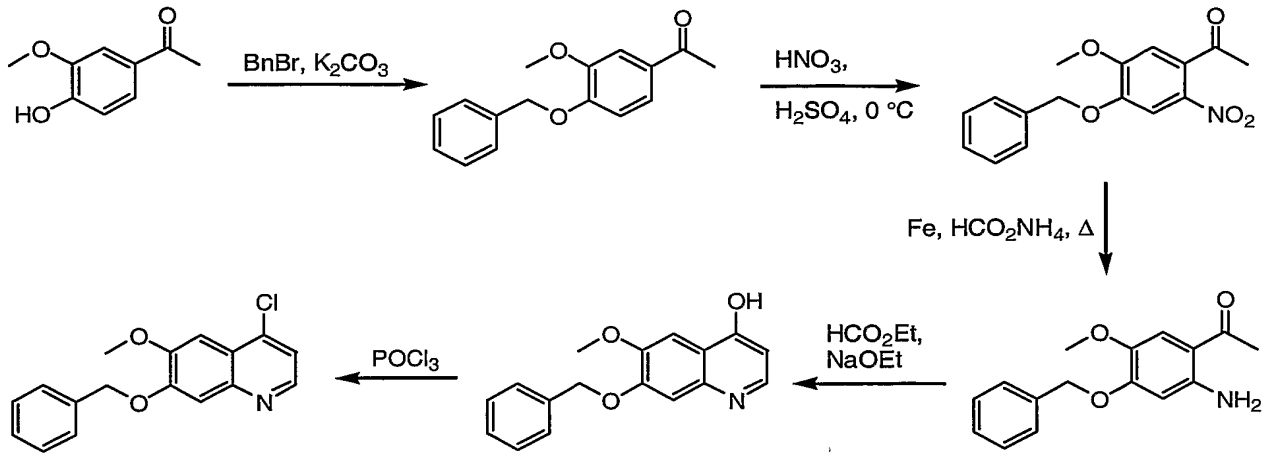
The EtOAc solution was washed with water, and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 900 mg (89%) of the crude product (90% purity by analytical HPLC), which was used in the next reaction without further purification.

Example 31



[0324] N-(4-{[7-{[2-(Diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide (186 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was added 2-(diethylamino)ethanol (63 mg, 0.54 mmol), and PPh_3 (141 mg, 0.54 mmol). DIAD (109 mg, 0.54 mmol) was then added as a CH_2Cl_2 (1 mL) solution. The resulted solution was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. To the residue was added 1 N HCl (50 mL), and it was washed with EtOAc (50 mL x 2). The aqueous phase was basified by adding 15% NaOH aqueous solution until pH =11-13, and then extracted with ether (50 mL x 2). The combined organic layer was dried (MgSO4), and concentrated in vacuo. The residue was purified on preparative HPLC to give N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide (74 mg, 34%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (br s, 1 H), 10.02 (br s, 1 H), 8.47 (d, J = 5.2 Hz, 1 H), 7.91 (br d, J = 13.9 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.55-7.50 (m, 1 H), 7.52 (s, 1 H), 7.50-7.40 (m, 1 H), 7.41 (s, 1 H), 7.16 (br t, J = 8.7 Hz, 2 H), 6.41 (br d, J = 4.7 Hz, 1 H), 4.18 (t, J = 6.0 Hz, 2 H), 3.94 (s, 3 H), 2.87 (br t, J = 6.3 Hz, 2 H), 2.59 (q, J = 7.1 Hz, 4 H), 1.47 (br s, 4 H), 1.00 (t, J = 7.0 Hz, 6 H).

Example 32



[0325] 1-(4-Benzyloxy-3-methoxyphenyl)ethanone. A solution of 4-hydroxy-3-methoxyacetophenone (40 g, 240 mmol), benzyl bromide (31.4 mL, 260 mmol) and potassium carbonate (99.6 g, 360 mmol) in DMF (800 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-(4-benzyloxy-3-methoxyphenyl)ethanone (61 g, 99 %).

[0326] 1-(4-Benzyloxy-5-methoxy-2-nitrophenyl)ethanone. A stirred solution of 1-(4-benzyloxy-3-methoxyphenyl)ethanone (51.3 g, 200 mmol) in dichloromethane (750 mL) was cooled to 0 °C. Nitric acid (90 %, 14 mL, 300 mmol) was added dropwise to the cooled solution over 20 min. Sulfuric acid (96.2 %, 16.3 mL, 300 mmol) was then added dropwise over 40 min at 0 °C. Additional nitric acid (9.4 mL, 200 mmol) was added dropwise over 20 min. The reaction mixture was washed with water (3 x 200 mL), and saturated sodium bicarbonate (4 x 200 mL, or until neutral). The organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was recrystallized from DMF to give 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 60 %). ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.45-7.33 (m, 5H), 6.74 (s, 1H), 5.21 (s, 2H), 3.97 (s, 3H), 2.49 (s, 3H).

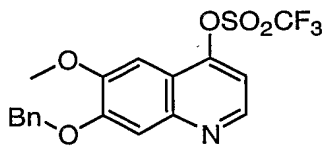
[0327] 1-(2-Amino-4-benzyloxy-5-methoxyphenyl)ethanone. A mixture of iron powder (27 g, 0.48 g atoms), ammonium formate (31 g, 500 mmol), 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 120 mmol), toluene (500 mL) and water (500 mL) was heated to reflux overnight. The mixture was filtered through celite and washed with ethyl acetate. The combined organic layers were washed with water and brine. The organic layer was

dried over Na_2SO_4 and concentrated to afford 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 90 %). ^{1}H NMR ($CDCl_3$): δ 7.41-7.30 (m, 5H), 7.13 (s, 1H), 6.16 (br s, 2H), 6.10 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H), 2.51 (s, 3H). LC/MS (M+H = 272).

[0328] 7-Benzyloxy-6-methoxyquinolin-4-ol. Sodium ethoxide (74.8 g, 1.1 mol) was added to a solution of 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 108 mmol) in DME (700 mL) and stirred for 30 min. Ethyl formate (44 mL, 540 mmol) was added and the mixture was stirred overnight (in case of incomplete reaction, additional sodium ethoxide can be added and the reaction monitored by LC/MS). After the reaction was complete, the mixture was diluted with water (40 mL) and acidified to neutral pH with 1M HCl. The solid was filtered, washed with water and dried to afford 7-benzyloxy-6-methoxyquinolin-4-ol (22 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.7 (br s, 1H), 7.70 (s, 1H), 7.49-7.46 (t, 1H), 7.43-7.41 (br d, 2H), 7.37-7.33 (t, 2H), 7.30-7.28 (d, 1H), 6.84 (s, 1H), 6.21-6.19 (d, 1H), 5.21 (s, 2H), 3.96 (s, 3H). LC/MS (M+H = 282).

[0329] 7-Benzyloxy-4-chloro-6-methoxyquinoline. Phosphorus oxychloride (300 mL) was added to 7-benzyloxy-6-methoxyquinolin-4-ol (40 g, 140 mmol) and the mixture heated to reflux for 2 h. The mixture was carefully poured into a mixture of ice and sodium carbonate. The solution was adjusted to pH 8 with the addition of solid sodium bicarbonate and stirred at room temperature overnight. The solid was filtered and washed with water and dried to give 7-benzyloxy-4-chloro-6-methoxyquinoline as a pale brown solid (40.2 g, 95%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.61 (s, 1H), 7.57-7.37 (m, 8H), 5.32 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 152.4, 151.5, 148.5, 146.2, 139.6, 137.0, 129.2, 128.8, 121.7, 120.4, 110.1, 101.9, 70.8, 56.5; IR (cm^{-1}): 2359, 2341, 1506, 1456, 1435, 1252, 1227, 1146, 999, 845, 752, 698, 667; LC/MS (M+H = 300).

Example 33



[0330] Trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester. To a dry 2L RBF containing 7-benzyloxy-6-methoxyquinolin-4-ol (75.3 g, 267 mmol) was added DCM (1 L), 4-dimethylaminopyridine (3.28 g, 26.8 mmol) and 2,6-lutidine (62 mL,